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Patentanmeldung Nr.	Patent application No.	Demande de brevet n°
	03104484.5	

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03104484.5
Demande no:

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Date of filing: 02.12.03
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Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Nitrooxyderivatives of antihypertensive drugs

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D/

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

(NP 0015)

Title

Nitrooxyderivatives of Antihypertensive drugs

The present invention relates to β-adrenergic blockers derivatives. More particularly, the present invention relates to β-adrenergic blockers nitrooxyderivatives, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache and vascular diseases.

β-adrenergic blockers (β-blockers) are widely used in the treatment of hypertension and cardiovascular diseases including angina pectoris, arrhythmias, acute myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure.

They work to block the effects of catecholamines at receptor sites in the heart, but they differ somewhat in their ability to block receptors in the blood vessels and lungs . Selective β-blockers have their major actions on the heart, some others are weak stimulators of the β-receptor while still blocking the major actions of catecholamines, some block both the β_1 and β_2 receptors in the heart and those in the blood vessels and have no stimulatory activity and some block other cathecolamine receptors that can lead to further vascular effects on blood vessels.

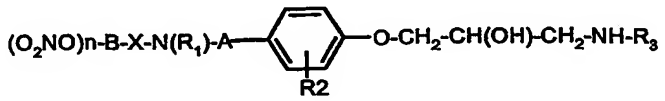
Several side effects are associated with this class of drugs such as muscle fatigue, sleep disturbances, decreased heart rate, hypotension, cold extremities, bronchospasm in asthmatic patients, hypoglicemia , increased in plasma lipids.

Moreover, abrupt withdrawal after long-term treatment with β-blockers has to be avoided, because an increased sensitivity to β-adrenergic system develops

U.S. Pat. No. 6,242,432 discloses derivatives of formula $A\text{-}(X_1\text{-}NO_2)_{to}$ having an antithrombotic activity, wherein A is the residue of a β-adrenergic blocker, X_1 is a bivalent connecting bridge and t_o is 1 or 2. The invention is limited to particular residues of β-adrenergic blockers.

U.S. Pat . No 5,502,237 and U.S. Pat. No 5,639,904 disclose derivatives of formula $R_1\text{-Ar-O-CH}_2\text{-CH(OH)-CH}_2\text{-NH-CH(CH}_3)_2$ used for the treatment of cardiovascular affections, wherein R_1 is a chain having at least one nitrooxy group as substituent.

U.S. Pat. No. 4,801,596 discloses aminopropanol derivatives of formula



that can be used for prophylaxis and/or treatment of heart and circulatory diseases, wherein R_3 is an alkyl or a nitrooxyalkyl radical containing 3 to 8 carbon atoms.

It was an object of the present invention to provide new β-adrenergic blockers nitrooxyderivatives having a significantly improved overall pharmacological profile as compared to native β-blockers that are able not only to eliminate or at least reduce the side effects associated with their parent compounds, but also having an improved pharmacological activity and tolerability.

It has been so surprisingly found that the β-adrenergic blockers nitrooxyderivatives of the present invention have a better pharmacological activity and organ protection properties, enhanced effects as anti-inflammatory, and on renal functions. In addition, they are effective in other pathologies including atherosclerosis, diabetes, peripheral vascular diseases (PVD).

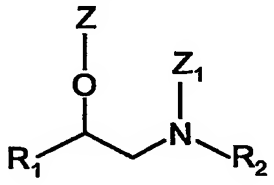
In particular, it has been recognized that the β-adrenergic blockers nitrooxyderivatives of the present invention, differently from the above mentioned compounds of the prior art, exhibit an improved activity on the cardiovascular system and enhanced tolerability and can be employed for treating or preventing hypertension, cardiovascular diseases, glaucoma, migraine headache and vascular diseases.

Object of the present invention are β-adrenergic blockers nitrooxyderivatives of general formula (I):

$$A\text{-}(Y\text{-}ONO_2)_s$$

and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, wherein s is an integer equal to 1 or 2;

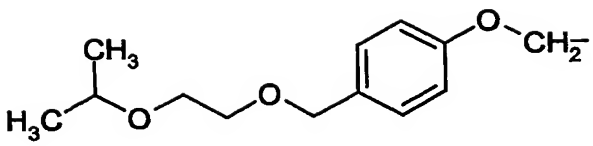
A is selected from the following β-adrenergic blocker residues of formula (II):



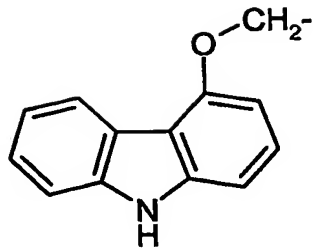
(II)

wherein

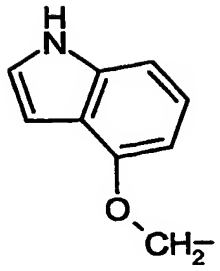
R_1 is selected from the group consisting of:



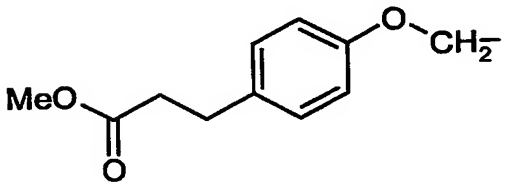
(IIa)



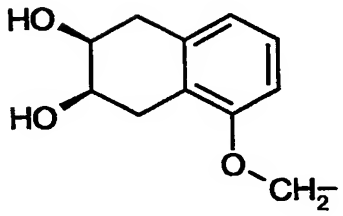
(IIb)



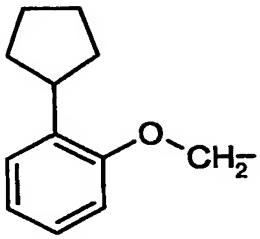
(IIc)



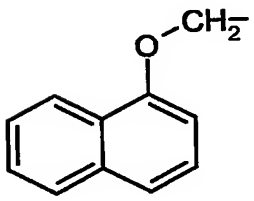
(IId)



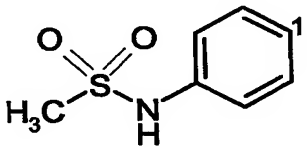
(IIe)



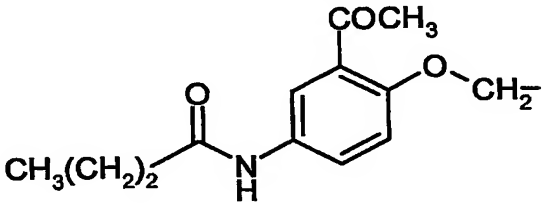
(IIf)



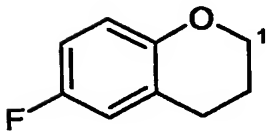
(IIg)



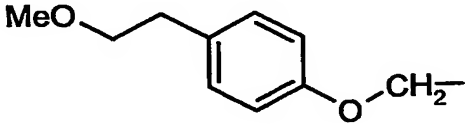
(IIh)



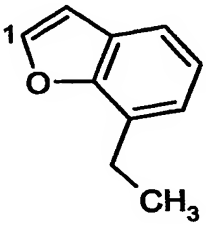
(IIi)



(IIL)



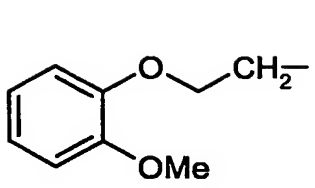
(IIm)



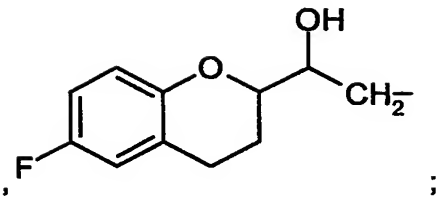
(IIn);

wherein the radicals R_1 of formulae (IIh), (IIL) and (IIn) are bound to A through the $[C]_1$ atom;

R_2 is selected from the group consisting of: $-CH(CH_3)_2$, $-C(CH_3)_3$ or



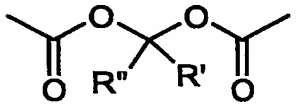
(IIIa)



(IIIb)

Z is H or is a group capable of binding Y selected from the group consisting of:

–C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl;

Z_1 is H or a –C(O)- capable of binding Y;

with the proviso that when s of formula (I) is 1 Z or Z_1 is H;

Y is a bivalent radical having the following meaning:

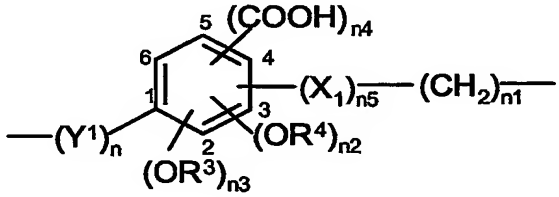
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is 0 or 1, and n1 is an integer from 1 to 20, preferably from 1 to 10;

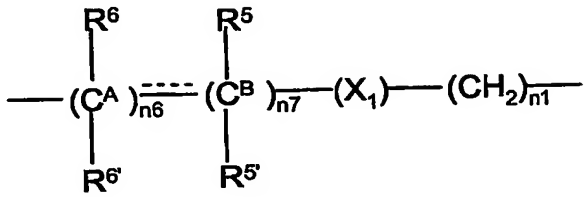
n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 1;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxigen, sulfur or NH;

d)



(VIII)

wherein:

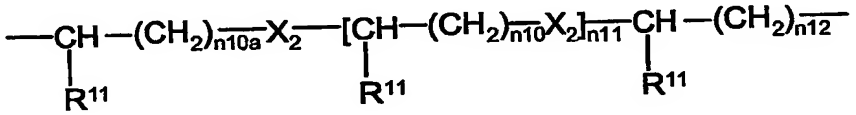
n1a is an integer from 1 to 20, preferably from 1 to 10;

X_1 is as above defined;

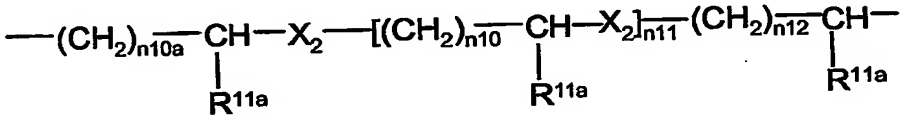
n6 is an integer from 1 to 20 and n7 is an integer from 0 to 20, R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $–ONO_2$ group is linked to a $–(CH_2)-$ group;

e)



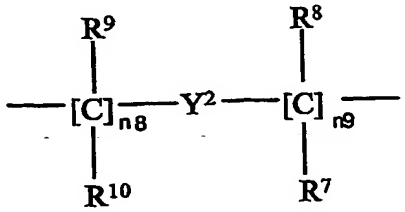
(VIII)



(IX)

wherein X_2 is O or S, n10a, n10 and n12 are integer independently selected from 0 to 20, n10a is preferably selected from 0 to 10, n10 and n12 are preferably selected from 1 to 10, and n11 is an integer from 0 to 6, preferably from 0 to 4, R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H, R^{11a} is CH_3 or nitrooxy group;

f)



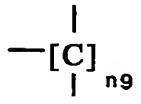
wherein

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^9, R^{10}, R^8, R^7 are H;

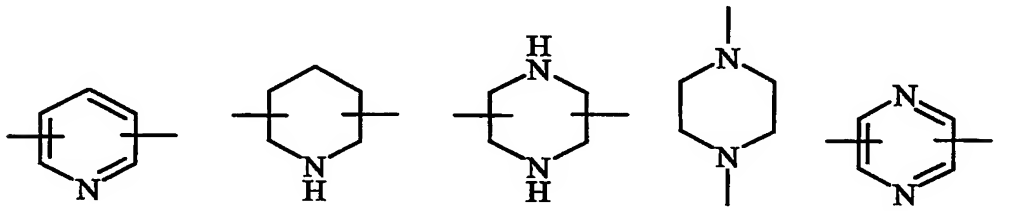
wherein the $-ONO_2$ group is linked to



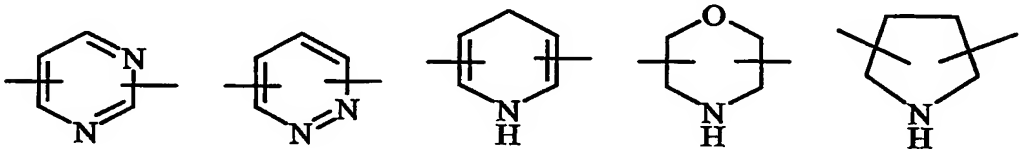
wherein n9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

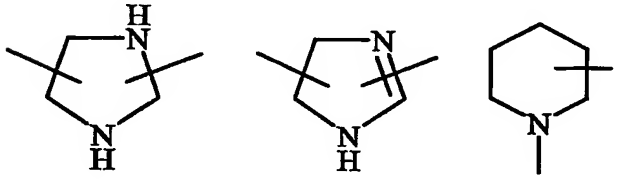
and is selected from the group consisting of



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)



(Y11) (Y12) (Y13)

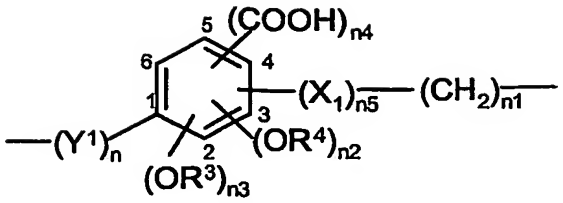
Preferred compounds are those of formula (I) wherein:

s and A are as above defined;

Y is a bivalent radical having the following meaning:

1) straight C_1-C_{10} alkylene, preferably C_3-C_5 alkylene;

2)



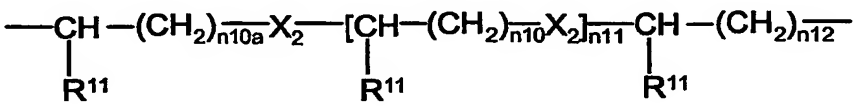
(IV)

wherein the $-ONO_2$ group is bound to $(CH_2)_{n1}$;

n, n2, n3, n4, n5 are equal to 0, n1 is 1 and the $-(CH_2)_{n1}-$ group is bound to the phenyl ring through the $[C]_2$ or $[C]_3$ or $[C]_4$;

or n, n2, n5 are 1, n3 and n4 are equal to 0, and n1 is 3, Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0, X_1 is $-WC(O)-$ wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$;

3)

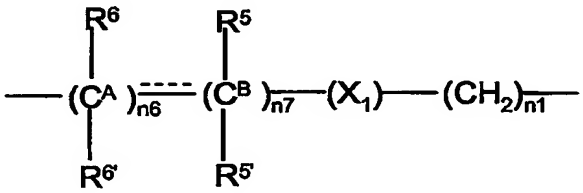


(VIII)

wherein

X_2 is O or S, and n10a and n11 are 0, n12 is 1 and R^{11} is H and the $-ONO_2$ group is bound to $(CH_2)_{n12}$;

4)



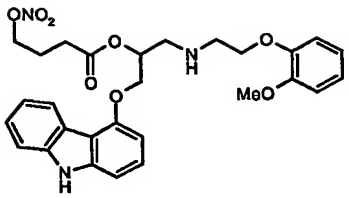
(VIII)

wherein

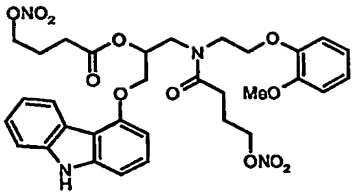
the $-ONO_2$ is bound to the $-(CH_2)_{n1}-$ group;

n1 is 3, n6 and n7 are 1, X_1 is $-WC(O)-$ wherein W is sulfur, R^5, $R^{5'}$ and $R^{6'}$ are H, R^6 is $NHCOCH_3$;

Preferred compounds of formula (I) according to the present invention are the following:



(1),



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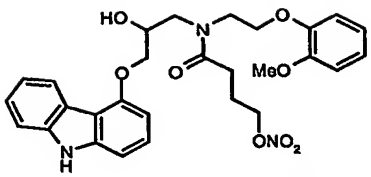
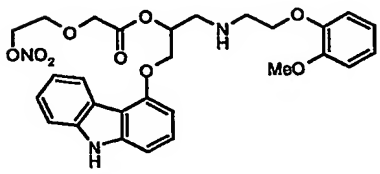


(3)



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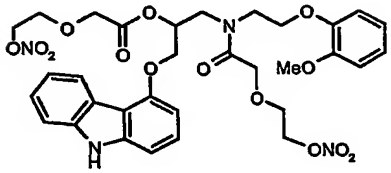

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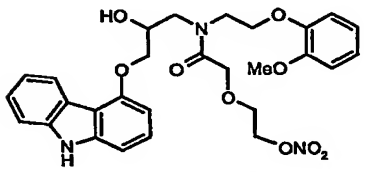

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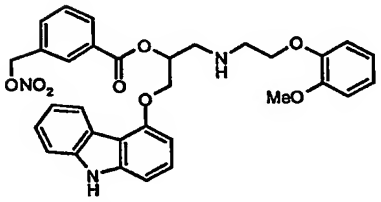

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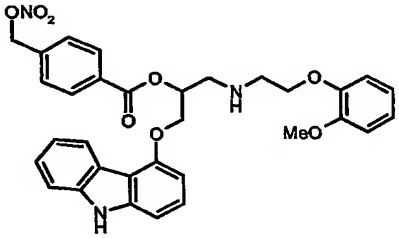

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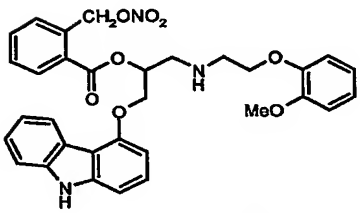

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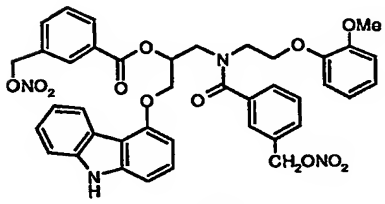

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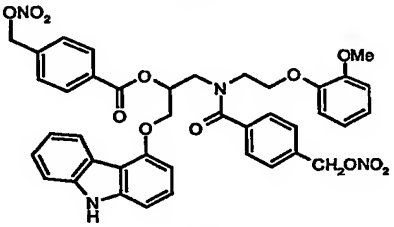

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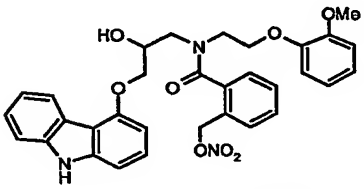

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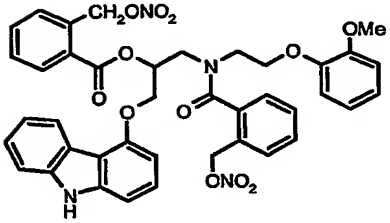

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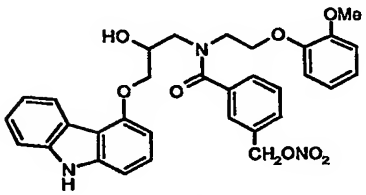

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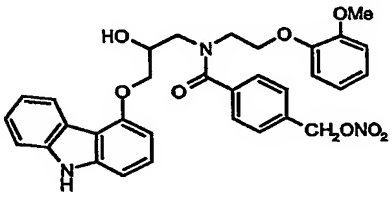

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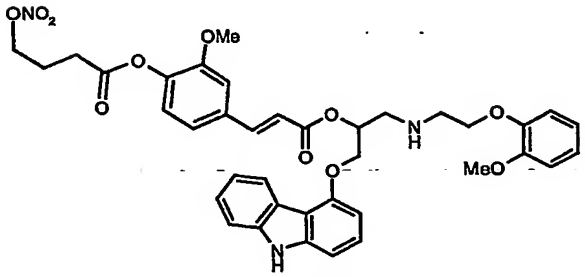

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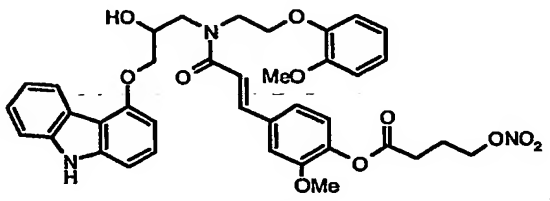

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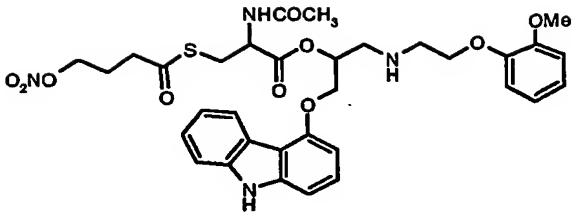

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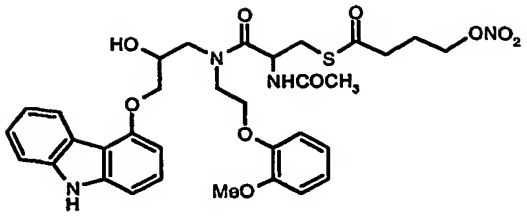

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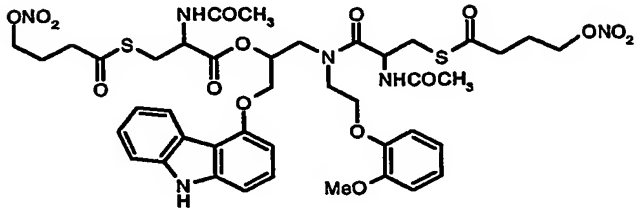

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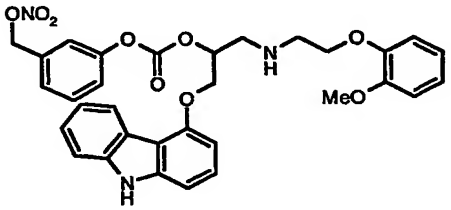

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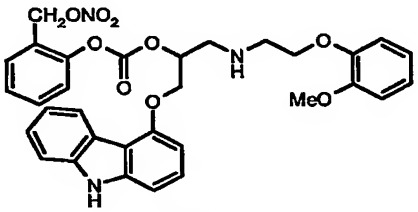

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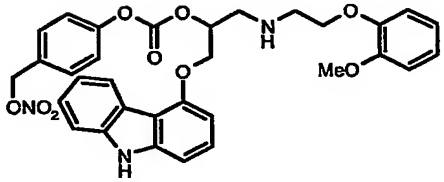

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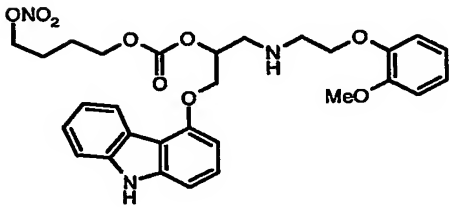

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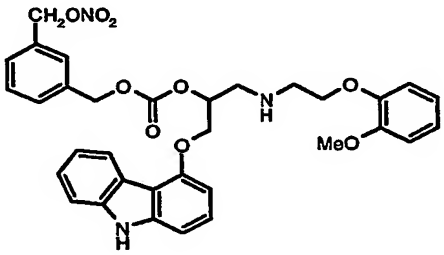

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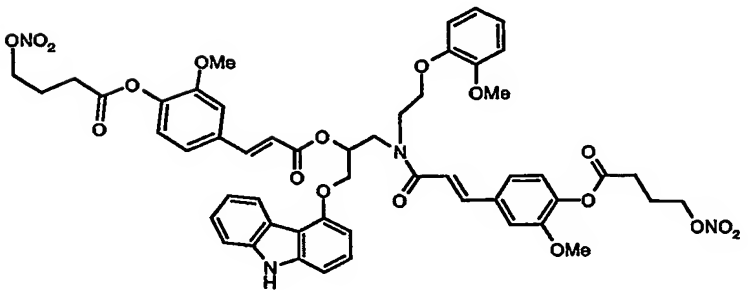

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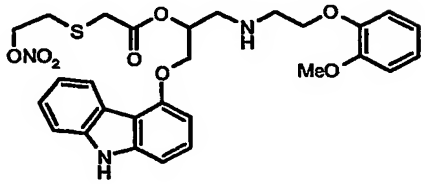

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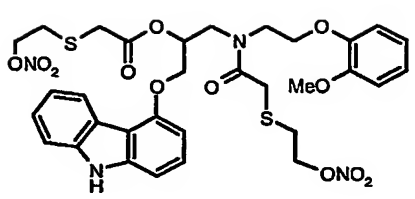

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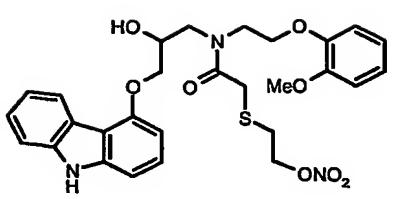

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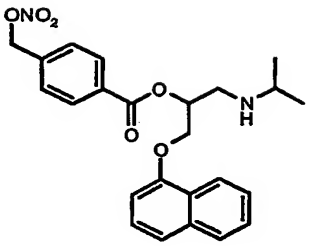

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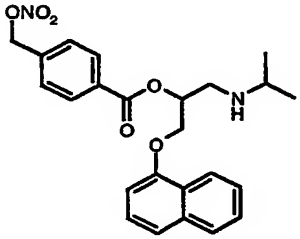

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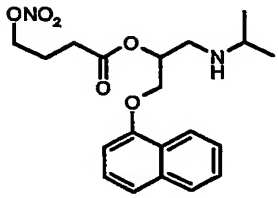

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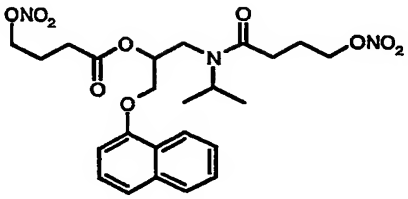

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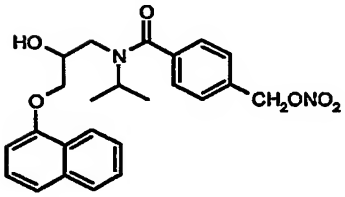

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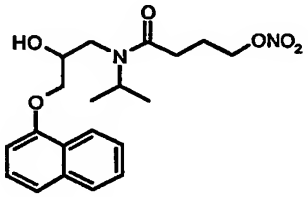

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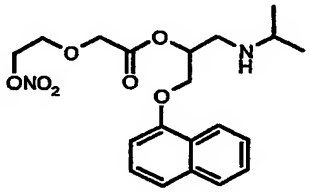

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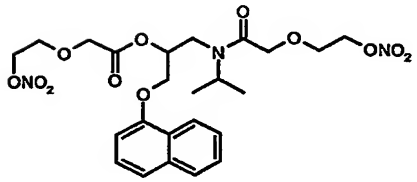

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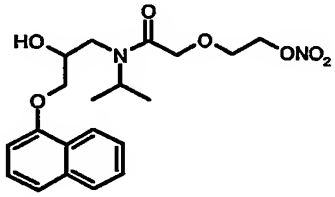

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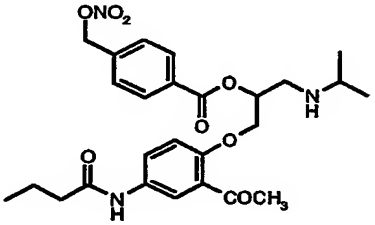

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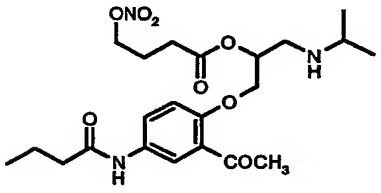

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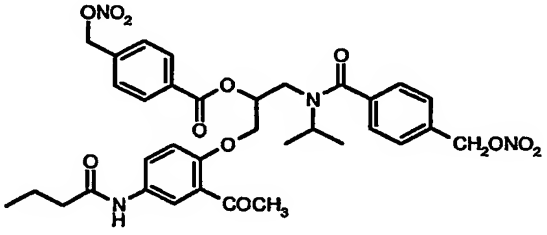

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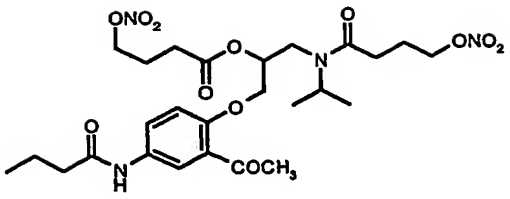

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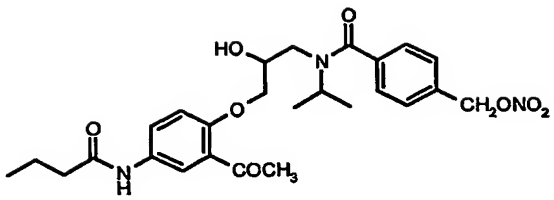

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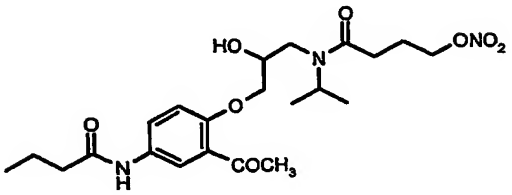

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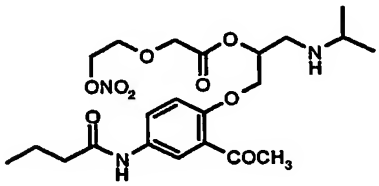

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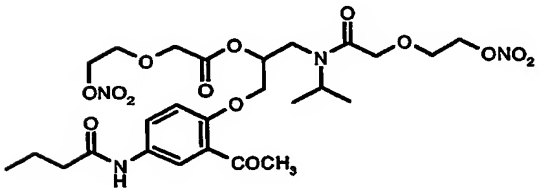

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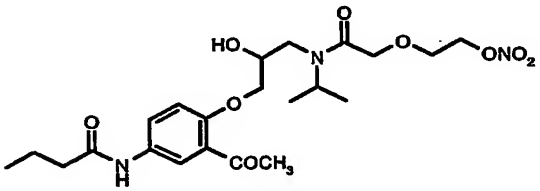

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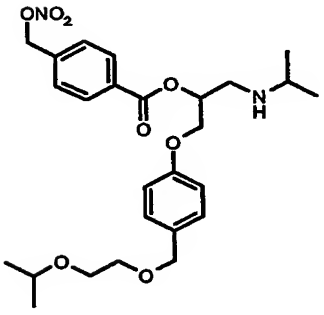

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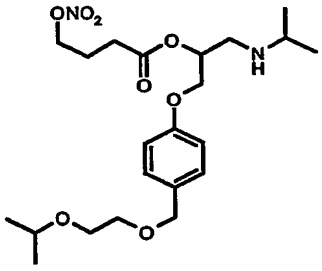

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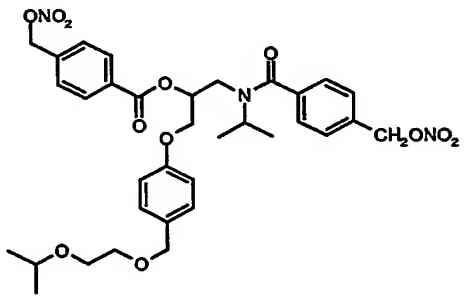

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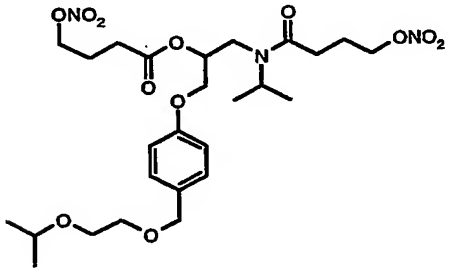

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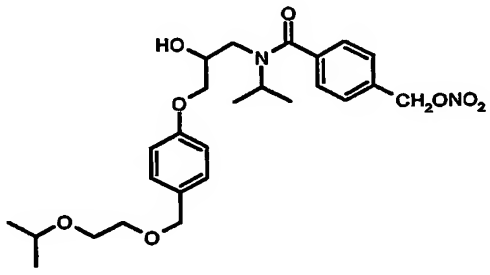

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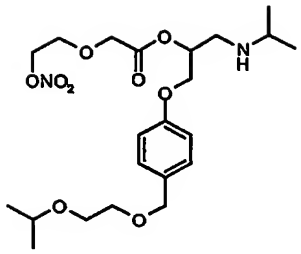

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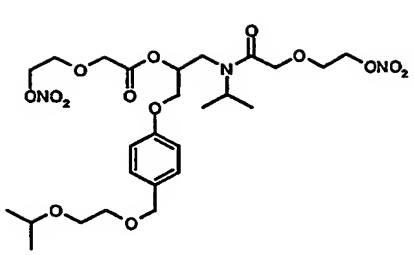

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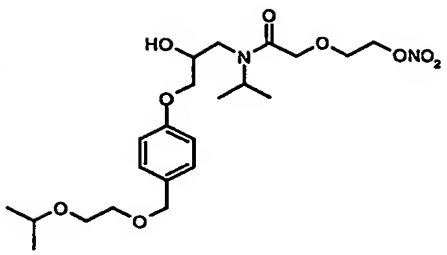

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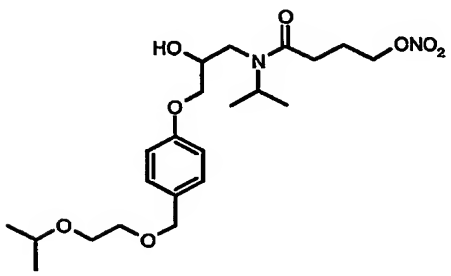

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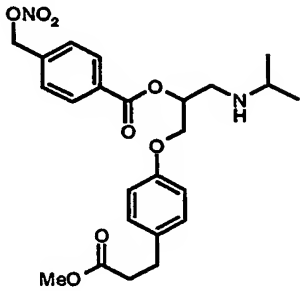

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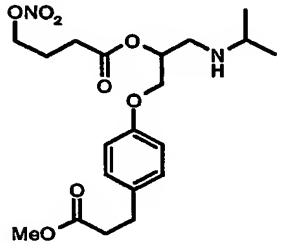

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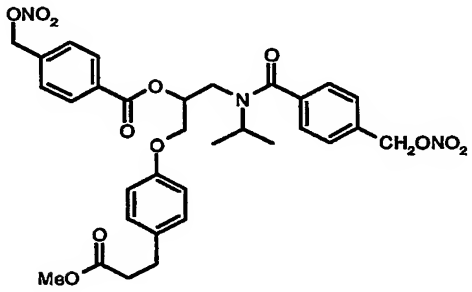

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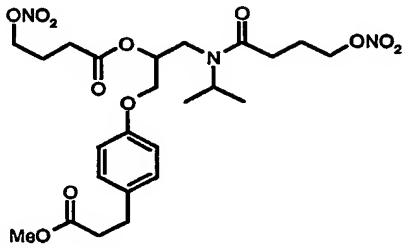

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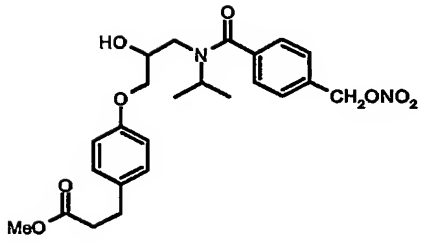

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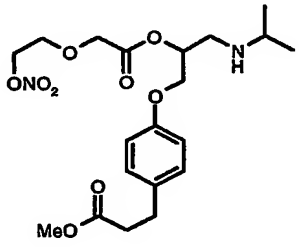

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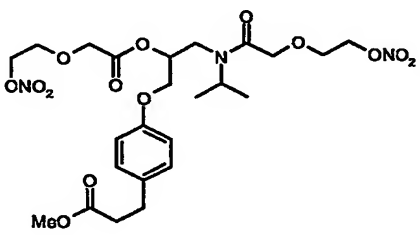

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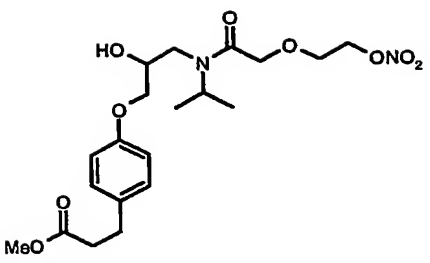

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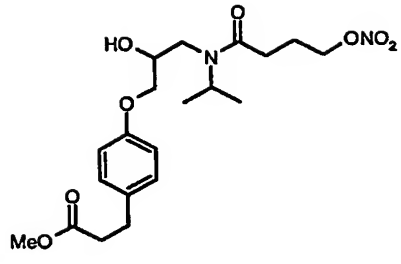

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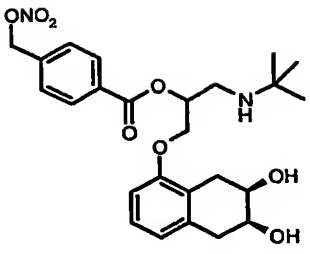

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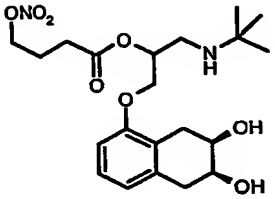

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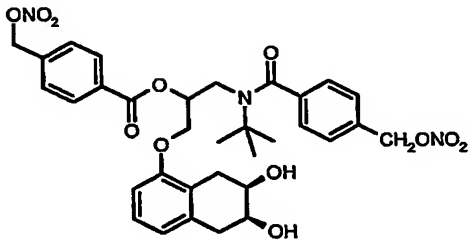

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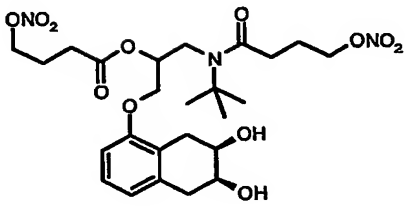

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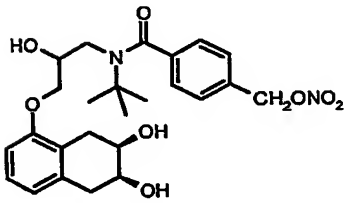

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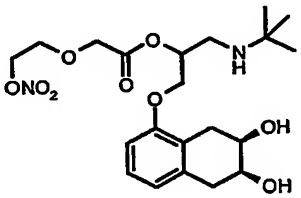

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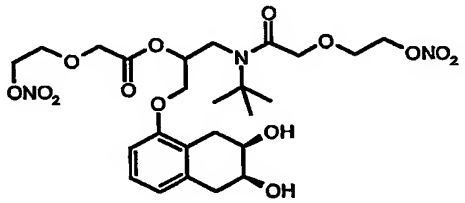

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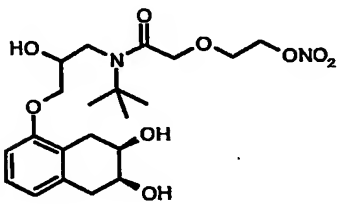

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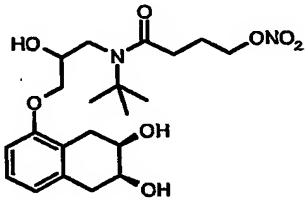

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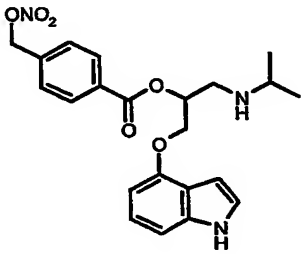

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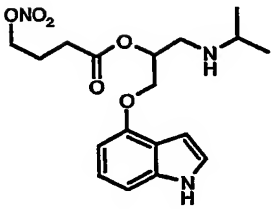

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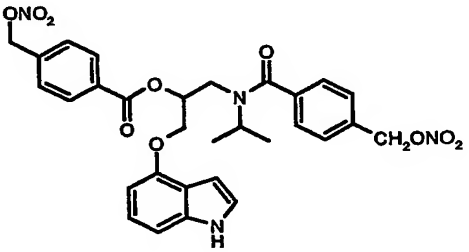

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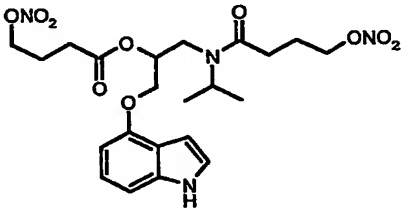

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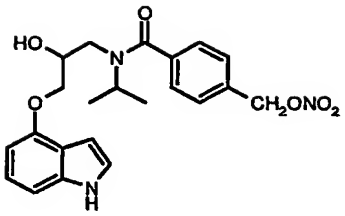

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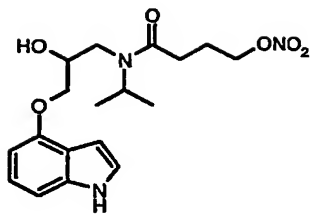

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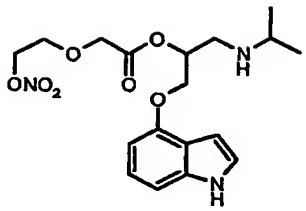

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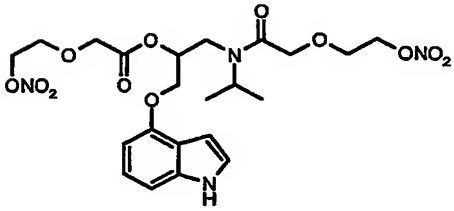

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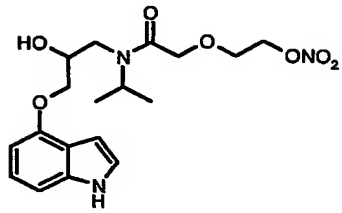

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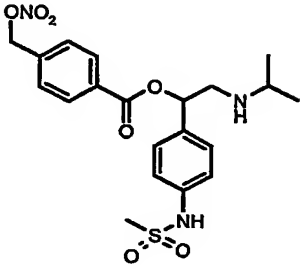

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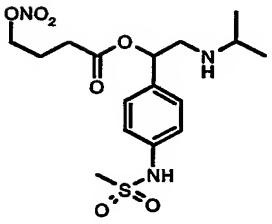

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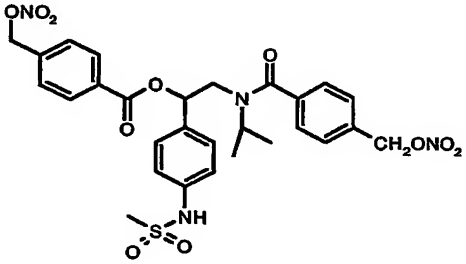

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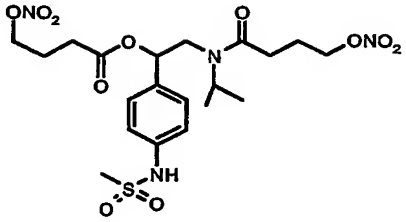

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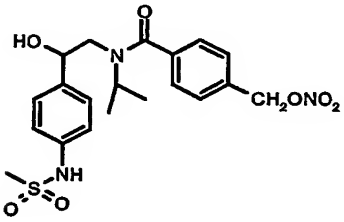

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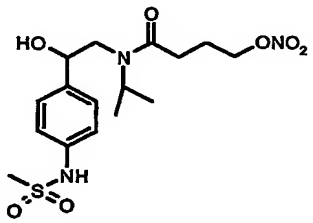

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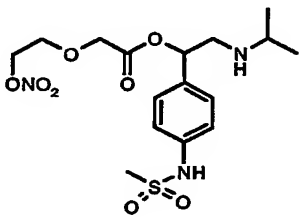

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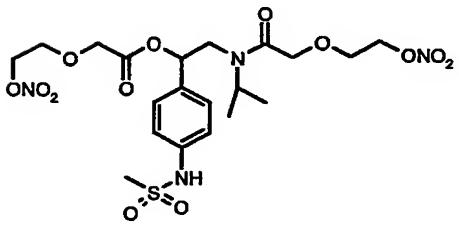

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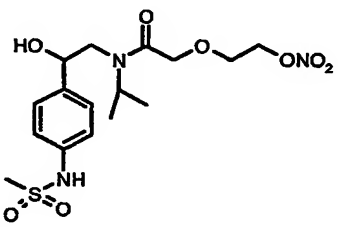

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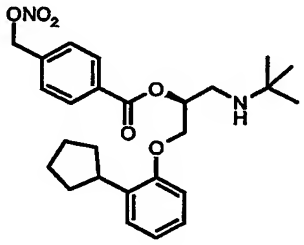

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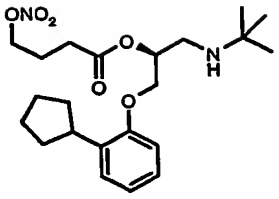

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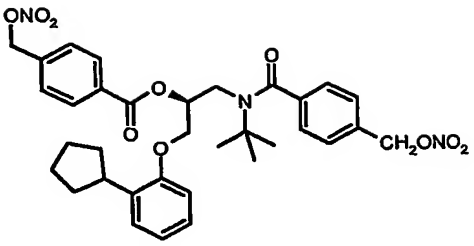

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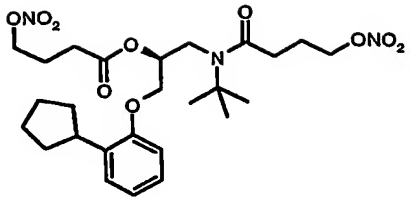

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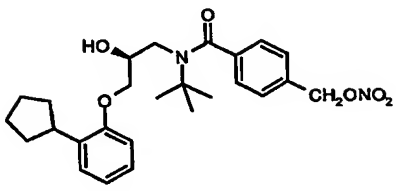

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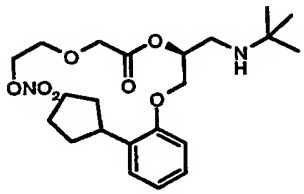

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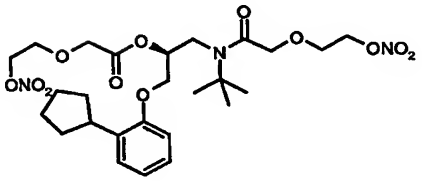

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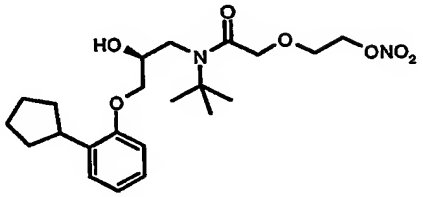

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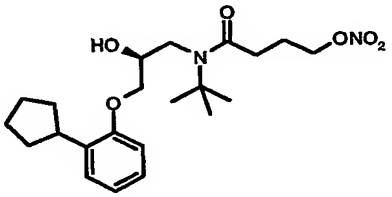

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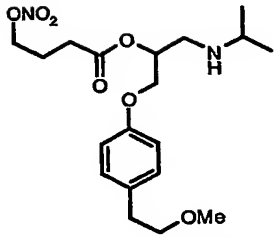

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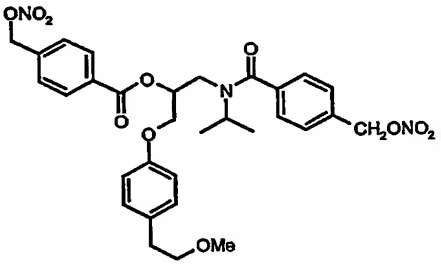

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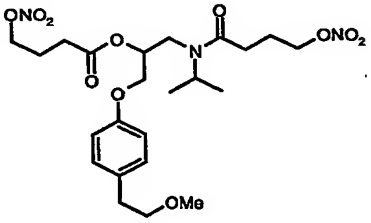

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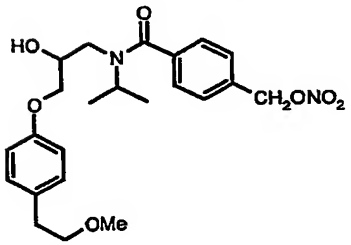

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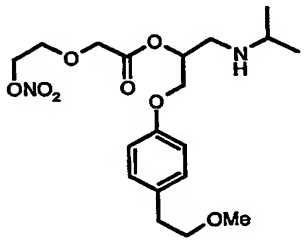

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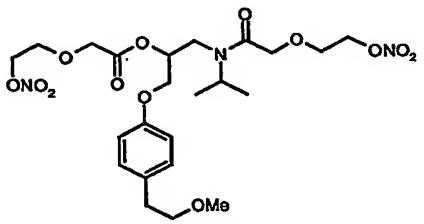

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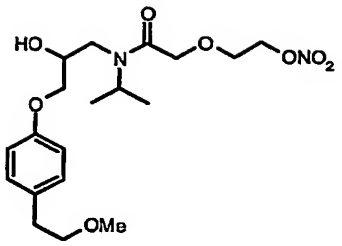

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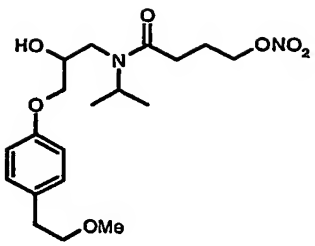


(109)

Examples of "straight or branched C_1-C_{20} alkylene" include, but are not limited to, methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of pharmaceutical acceptable organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of pharmaceutical acceptable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The compounds and compositions of the present invention can be administered by any available and effective delivery system including but not limited to, orally, bucally, parenterally, by inhalation spray, by topicall application, by injection, transdermally, or rectally (e.g. by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion technique.

Solid dosage forms for oral administration can include for example capsule, tablets, pills, powders, granules and gel. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage form can also comprise, as normal practice, additional substance other than inert diluent, e.g., lubricating agent such as magnesium stearate.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents.

The composition of this invention can further include conventional excipients, i.e., pharmaceutical acceptable organic or inorganic substances which do not deleteriously react with the active compounds.

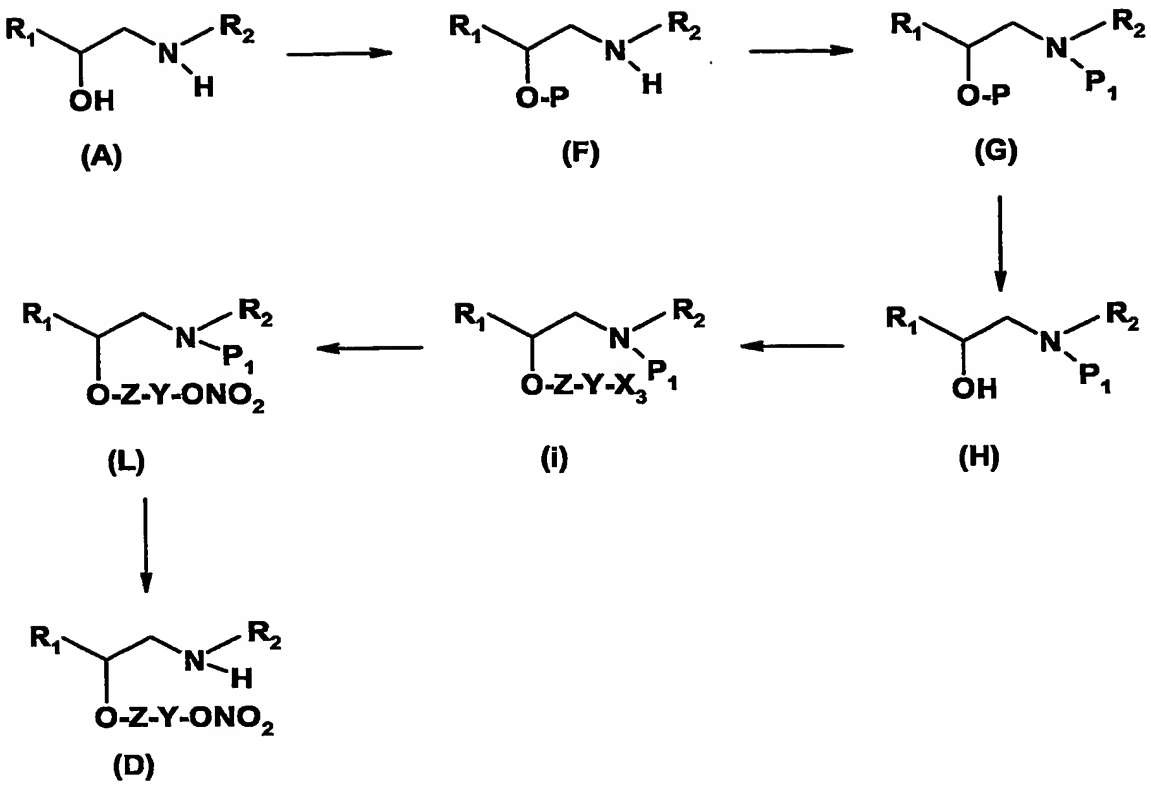
The doses of β-adrenergic blockers nitrooxyderivatives can be determinated by standard clinique technique and are in the same ranges or less than as described for commercially available compounds as reported in the: Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 58th Ed., 2004; The pharmacological basis of therapeutics, Goodman and Gilman, J. G. Hardman, L. e. Limbird, 20th Ed.

EXPERIMENTAL

Synthesis procedure

Compounds of the invention can be synthesized as shown in Schemes 1 to 6. Compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 1-3 as compounds of formula D, wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is –C(O)- and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof , can be prepared as outlined in Schemes 1 -3.

Scheme 1



Compounds of formula (i) wherein R_1, R_2, Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom preferably Cl, Br and I, are converted to compounds of formula (L) wherein R_1, R_2, P_1, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature to the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (H) wherein R_1, R_2, Z, $P_1$and Y are as above defined, are converted to the esters of formula (i) wherein R_1, R_2, Y, Z, X_3 and P_1 are as above defined, by reaction with an appropriate acid (Q1) of formula X_3-Y-COOH wherein Y and X_3 are as above defined. The reaction is generally carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C to 50°C in presence of a dehydrating agent such as dycyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)

carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

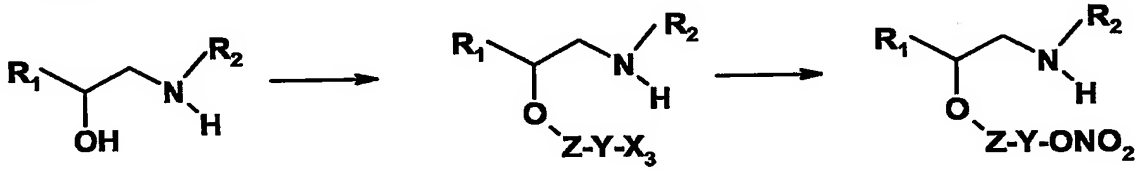
The compounds of formula (H) wherein R_1, R_2 and P_1 are as above defined, can be obtained by deprotecting the hydroxylic group of the compounds of formula (G) wherein R_1, R_2 are as above defined and P is a hydroxylic protecting group such as silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980. Fluoride ion is the preferred method for removing silyl ether protecting group.

The compounds of formula (G) wherein R_1, R_2, P and P_1 are as above defined, can be obtained by reacting the compounds of formula (F) wherein R_1, R_2 and P are as above defined with a suitable amine protecting group (P_1) as above described.

The alcohol group of the compounds of formula (A) wherein R_1, R_2 are as above defined, is protected to afford the compounds of formula (F) wherein R_1, R_2 are as above defined Preferred protecting group for the alcohol moiety are silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available, the acids of formula X_3-Y-COOH wherein X_3 is as above defined, are commercially available.

Scheme 2



(A) (B) (D)

Compounds of formula (B) wherein R_1, R_2, Z, Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D) wherein R_1, R_2, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (B) wherein R_1, R_2, Z, Y and X_3 are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl chloride (Q) of formula X_3-Y-C(O)Cl, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The esterification is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base

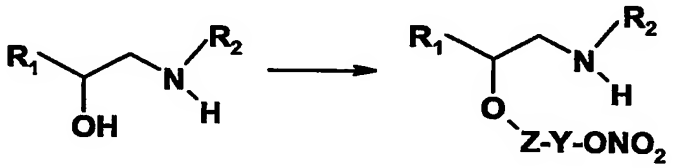
as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (B) can be obtained by reaction of compounds of formula (A) with an acid (Q1) of formula X_3-Y-C(O)OH in the presence of a dehydrating agent as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalyst, such as N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available

Scheme 3



(A) (D)

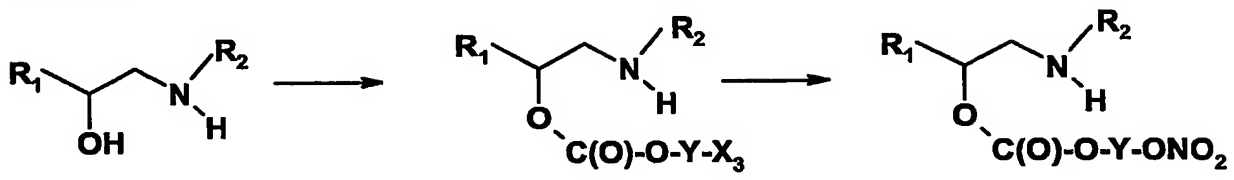
Alternatively the compounds of formula (D) can be obtained as described below. The compounds of formula are converted to the compounds (D) by reaction of hydroxy group with a nitrooxy derivative, containing activated acylating group, of formula Cl(O)C-Y-ONO_2.

The nitrooxy compounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from –50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 4 as compounds of formula (D1), wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is -C(O)O- and Z_1 is H, the enantiomers,

diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Scheme 4.

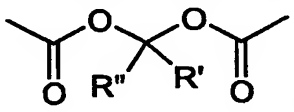
Scheme 4



The compounds of formula (B1) wherein R_1, R_2, Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D1) wherein R_1, R_2, and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

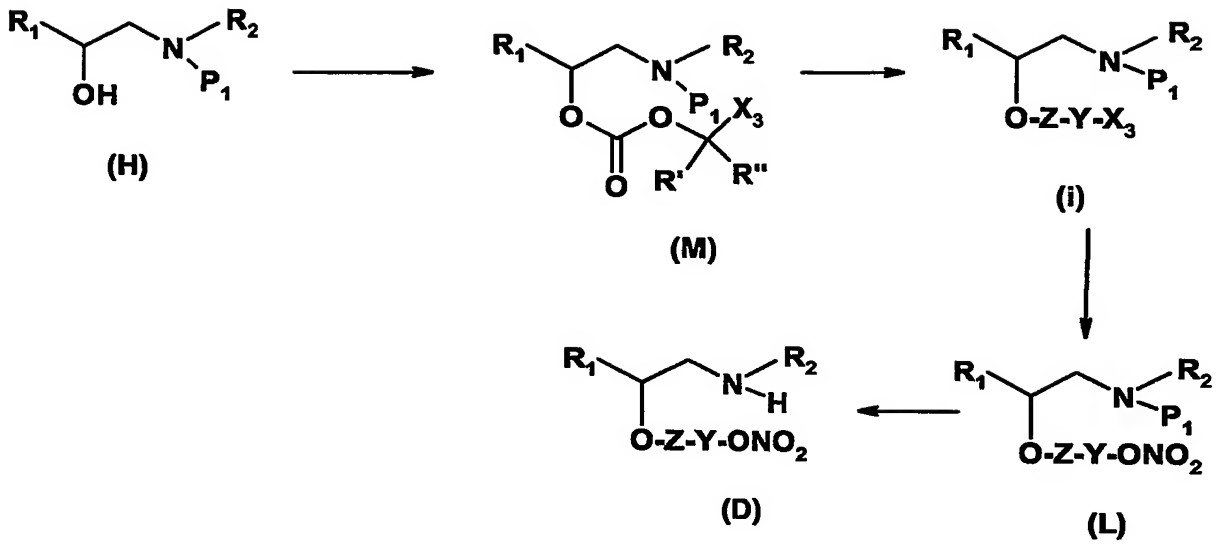
The compounds of formula (A) wherein R_1 and R_2 are as above defined are converted to the compounds (B1) by reaction with an appropriate compound (Q2) having formula X_3-Y-OC(O)Cl wherein X_3 is Cl, Br or I, and Y is as defined above. The reaction is generally carried out in presence of a base in an aprotic polar or non-polar solvent such as THF or CH_2Cl_2 at temperature range between 0°-65°C or in a double phase system H_2O/Et_2O at temperature range between 20°- 40°C.

The compounds of formula (Q2) are commercially available or can be obtained from the corresponding alcohols by reaction with triphosgene in presence of an organic base.

The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 5 as compounds of formula (D), wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is 

wherein R' and R'' are H or straight or branched C_1-C_4 alkyl and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salts thereof, may be prepared as outlined in Scheme 5:

Scheme 5



The compounds of formula (i) wherein R_1, R_2, Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom such as Cl, Br and I, are converted to compounds of formula (L) wherein R_1, R_2, P_1, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (i) wherein R_1, R_2, Y, X_3, Z and P_1 are as above defined, can be obtained by reacting the compounds of formula (M) wherein R_1, R_2, P_1, R', R" and X_3 are as above defined, with an acid (Q1) of formula X_3-Y-COOH wherein X_3 is an halogen atom and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature range from 0°C and 50°C in the presence of a dehydrating agent such as dycyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

The reaction is complete within a time ranges from 30 minutes to 24 hours.

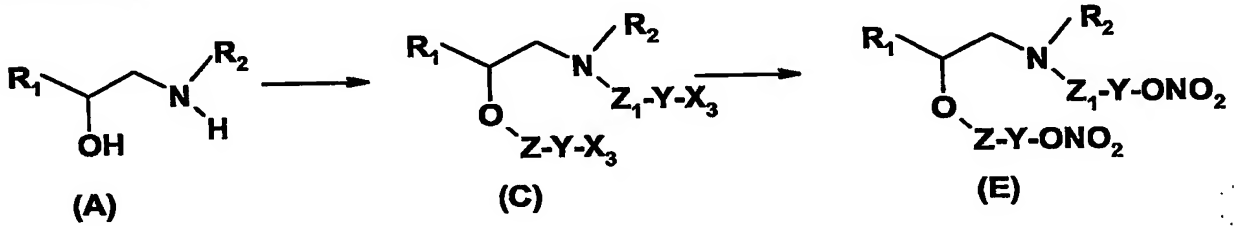
The compounds of formula (M) wherein R_1, R_2, P_1, R', R" and X_3 are as above defined, can be obtained by reacting the compounds the of formula (H) with a compound (S) of formula X_3-C(R')(R")-OC(O)X_3 wherein X_3 is an halogen atom. The reaction is carried out

in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from –5°C to 60°C or in a double phase system according to methods well known in the literature.

The amine group of the compounds (A) is protected to afford the compounds of formula (H) wherein P_1 is a suitable amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) The compounds (S) are commercially available.

The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 6 as compounds of formula (E), wherein s is 2, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z_1 and Z are –C(O)-, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be synthesized as shown in Scheme 6.

Scheme 6



Compounds of formula (C) wherein R_1, R_2, Z, Z_1 and Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (E) wherein R_1, R_2, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (C) wherein R_1, R_2, Z, Z_1, Y and X_3 are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl halide (Q) of formula X_3-Y-C(O)Cl, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (C) can be obtained by reaction of the compounds of formula (A) with an acid (Q1) of formula X_3-Y-COOH in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as N,N'-

dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available.

The compounds of formula (E) can also be obtained as described below. The compounds of formula A are converted to the compounds (E) by reaction with a nitrooxy derivative of formula $Cl(O)C\text{-}Y\text{-}ONO_2$ containing an activated acylating group.

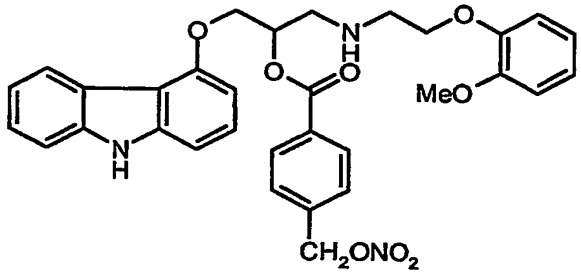
The nitrooxycompounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from –50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

Examples

The following non-limiting examples further describe and enable one of ordinary skilled in the art to make and use the present invention.

Example 1

4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate of formula (8).



(8)

1a. 4-(Chloromethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with water and the organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4 (Rf=0.2). The title product 0.27g was obtained as a white powder.

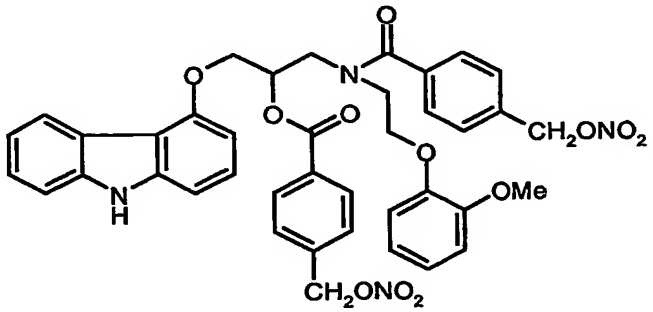
1b. 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]-2-propanoate

A solution of the product of Example 1a (0.27g, 0.48mmol) and silver nitrate (0.16g, 0.96mmol) in acetonitrile (30ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was treated with chloroform and water. The organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with ethyl acetate/n-hexane 6/4. The title product 0.03g was obtained as a white powder.

^{1}H-NMR (DMSO) δ (ppm): 11.25 (1H,s); 8.10(3H,m); 7.59-6.72(14H,m); 5.76(1H,m); 5.63 (2H,s); 4.52 (2H,m); 4.04 (2H,m); 3.67(3H,s); 3.62 (2H,m); 3.36 (2H,m); 3.22 (2H,m).

Example 2

4-(Nitrooxymethyl)benzoic acid 1- (9H -carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanoate of formula (11).



(11)

2a. 4-(Chloromethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-chloromethyl)benzoyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and

filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1 (Rf=0.42). The title product (0.06g) was obtained as a white powder.

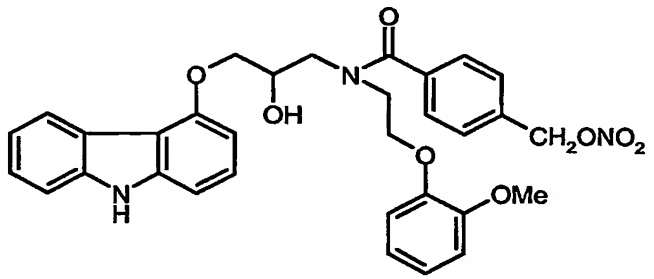
2b. 4-(Nitrooxymethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanoate

A solution of the product of example 2a (0.06g, 0.08mmol) and silver nitrate (0.06g, 0.32mmol) in acetonitrile (20ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with chloroform and water. The combined organic layer extracts were dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4. The title product 0.015g was obtained as a powder.

^{1}H-NMR (DMSO) δ (ppm): 11.24 (1H,s); 8.60-6.70 (18H,m); 7.59-6.72(14H,m); 6.18(1H,m); 5.62 (2H,s); 5.58 (2H,s); 4.80 (2H,m); 4.56 (2H,m); 4.30(2H,m); 4.07 (2H,m); 3.71 (3H,s).

Example 3

1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanol of formula (15)



(15)

3a. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-chloromethyl)benzoyl] amino]-2-propanol

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4 (Rf=0.42). The title product 1.05g was obtained as a white powder.

3b. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanol

A solution of the product of example 3a (1.0g, 1.78mmol) and silver nitrate (0,6g, 3.6mmol) in acetonitrile (100ml) was stirred at 65°C, in the dark, for 32 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with methylene chloride and water. The combined organic layer extracts were dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1. The title product 0.4g was obtained as yellow powder.

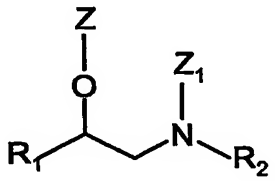
^{1}H-NMR (DMSO) δ (ppm): 11.24 (1H,s); 8.40-6.50 (13H,m); 5.61-5.36(2H,m); 5.51(1H,m); 4.50-3.71 (8H,m); 3.72 (3H,m).

CLAIMS

1. A compound of general formula A-(Y-ONO_2)$_s$ (I) and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof, wherein

s is an integer equal to 1 or 2;

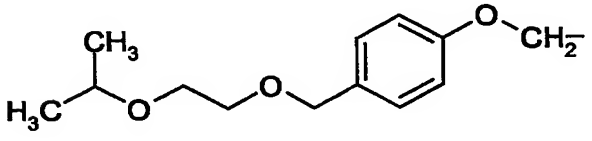
A is selected from the following β-adrenergic blockers residues of formula (II):



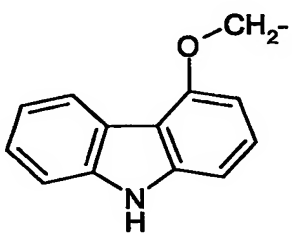
(II)

wherein

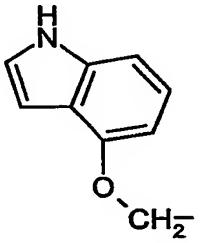
R_1 is selected from the group consisting of:



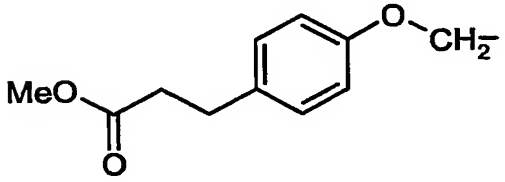
(IIa)



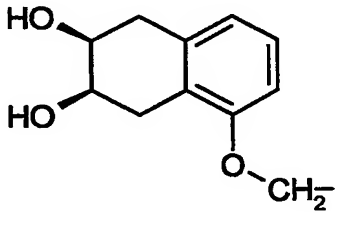
(IIb)



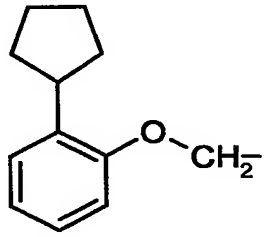
(IIc)



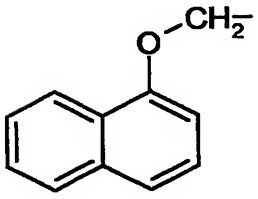
(IId)



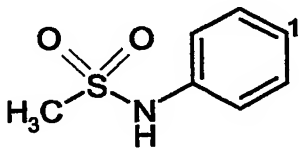
(IIe)



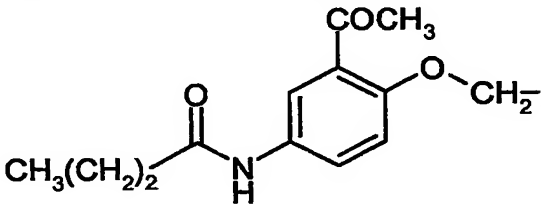
(IIf)



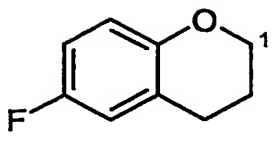
(IIg)



(IIh)



(IIi)



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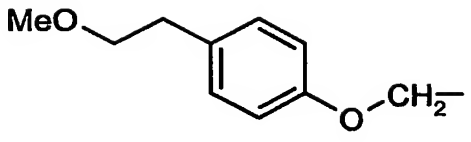

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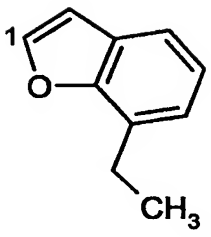
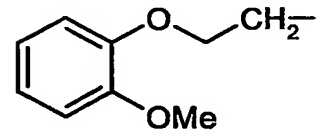


;

(IIL) (IIm) (IIn)

wherein R_1 of formulae (IIh), (IIL) and (IIn) are bound to A through the $[C]_1$ atom;

R_2 is selected from the group consisting of: $-CH(CH_3)_2$, $-C(CH_3)_3$ or



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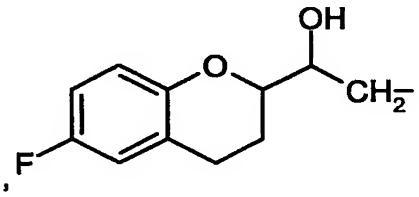
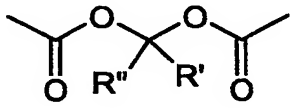


;

(IIIa) (IIIb)

Z is H or is a group capable of binding Y selected from the group consisting of:

–C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl;

Z_1 is H or a –C(O)- group capable of binding Y;

with the proviso that when s of formula (I) is 1, Z or Z_1 is H;

Y is a bivalent radical having the following meaning:

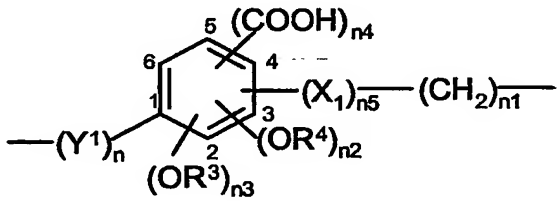
a)

- straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms;

c)



(IV)

wherein:

n is an integer from 0 to 20 and n1 is an integer from 1 to 20;

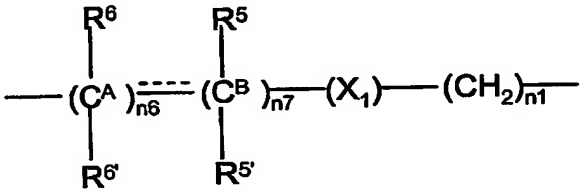
n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxigen, sulfur or NH;

d)



(VIII)

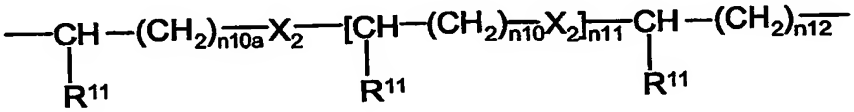
wherein:

n1 and X_1 are as above defined;

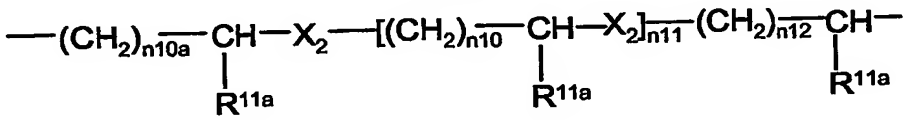
n6 is an integer from 1 to 20 and n7 is an integer from 0 to 20, R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $-ONO_2$ group is linked to the $-(CH_2)_{n1}-$ group;

e)



(VIII)



(IX)

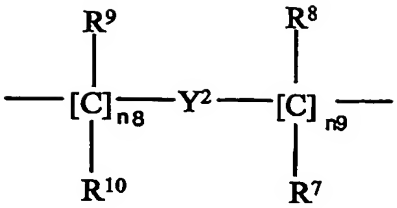
wherein X_2 is O or S, n10a, n10 and n12 are integer independently selected from 0 to 20,

n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or nitrooxy group;

R^{11a} is CH_3 or nitrooxy group;

f)



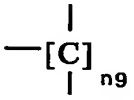
wherein:

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl;

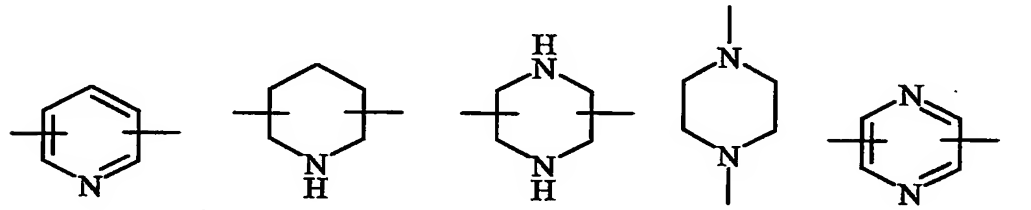
wherein the $-ONO_2$ group is linked to



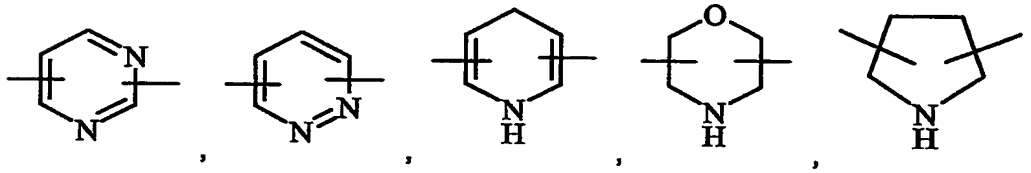
wherein n9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

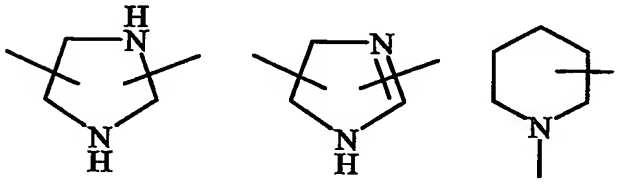
and is selected from the group consisting of:



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)



(Y11) (Y12) (Y13)

2. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein

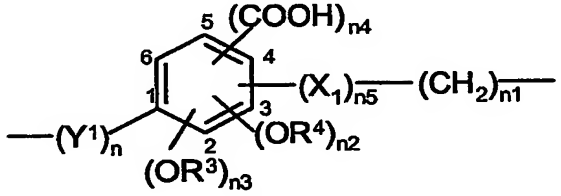
s is equal to 1 and Z_1 is H.

3. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Z is –C(O)-.

4. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein
Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

5. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 4 wherein
Y is a straight or branched C_1-C_{10} alkylene.

6. A compound and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein
Y is



(IV)

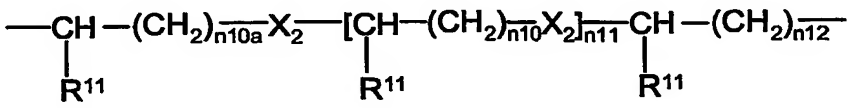
wherein
n is an integer from 0 to 20, and n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;
R^3 and R^4 are independently selected from H or CH_3;
Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20;
X_1 is –WC(O)- or –C(O)W-, wherein W is oxigen, sulfur or NH.

7. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 6 wherein n2, n3, n4, n5 are equal to 0, n is an integer from 0 to 20, Y^1 is CH_2.

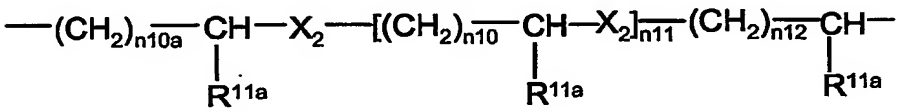
8. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 6 wherein n, n2, n5 are 1, n3 and n4 are equal to 0, and n1 is 3, Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0, X_1 is $-WC(O)-$ wherein W is oxigen and X_1 is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$.

9. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein

Y is



(VIII)



(IX)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

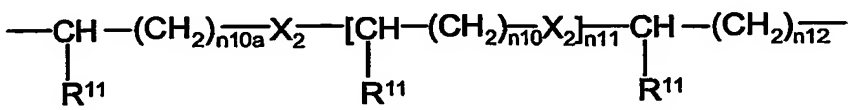
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

10. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 9 wherein

Y is



(VIII)

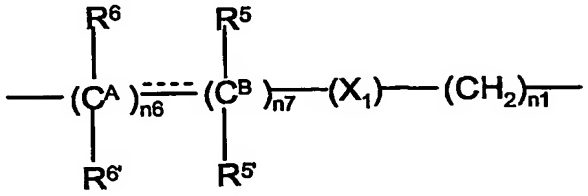
wherein

X_2 is O or S, n10a and n11 are 0, n12 is 1 and R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

11. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein

Y is



(VIII)

wherein:

n1 is an integer from 1 to 20;

X_1 is –WC(O)- or a –C(O)W-, wherein W is oxigen, sulfur or NH.

n6 is an integer from 1 to 20 and n7 is an integer from 0 to 20, R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

12. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 11 wherein

n1 is 3, n6 and n7 are 1;

X_1 is -WCO- wherein W is sulfur;

R^5, $R^{5'}$ and $R^{6'}$are H, R^6 is $NHCOCH_3$;

wherein the $–ONO_2$ group is bound to the $-(CH_2)_{n1}-$ group.

13. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Z is –C(O)O-.

14. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 13 wherein

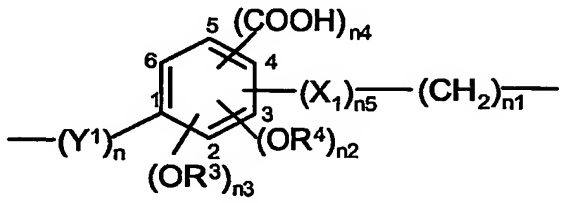
Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

15. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 14 wherein

Y is a straight or branched C_1-C_{10} alkylene.

16. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 13 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20, and n1 is an integer from 1 to 20;

n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

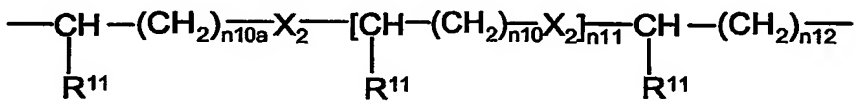
Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is $-WC(O)-$ or $-C(O)W-$, wherein W is oxigen, sulfur or NH.

17. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 16 wherein n2, n3, n4, n5 are equal to 0, n is an integer from 0 to 20, Y^1 is CH_2.

18. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 13 wherein

Y is



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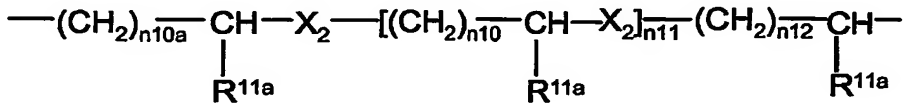


(IX)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

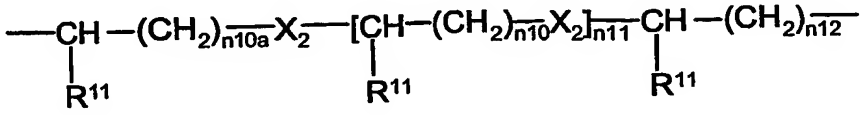
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

19. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 18 wherein

Y is



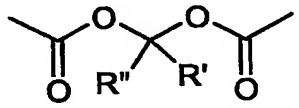
(VIII)

wherein

X_2 is O or S, n10a and n11 are 0, n12 is 1 and R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

20. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 2 wherein Z is



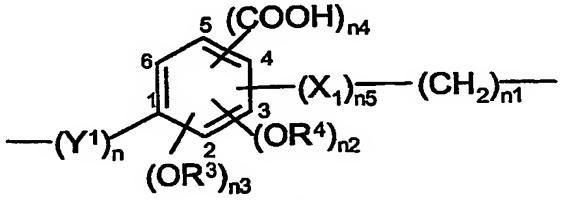
21. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10}alkyl)-ONO_2, $-O(C_1$-C_{10}alkyl)-ONO_2.

22. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 21 wherein Y is a straight or branched C_1-C_{10} alkylene.

23. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20, and n1 is an integer from 1 to 20;

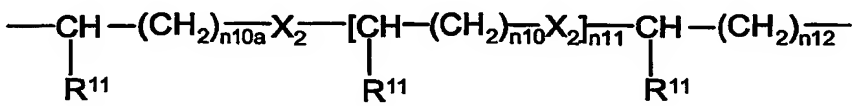
n2, n3, n4 and n5 are equal to 0;

Y^1 is $-CH_2-$;

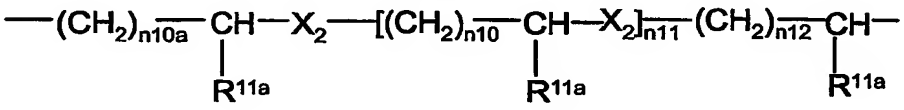
24. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 23 wherein n is 0 and n1 is 1.

25. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is



(VIII)



(IX)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

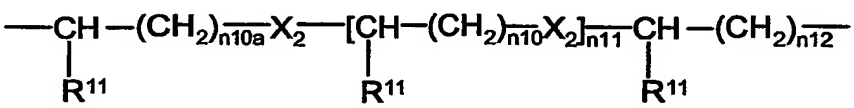
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

26. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 25 wherein

Y is



(VIII)

wherein

X_2 is O or S, n10a and n11 are 0, n12 is 1 and R^{11} is H;

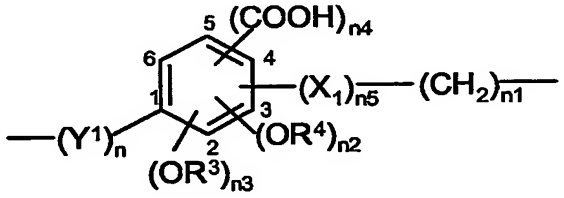
wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

27. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein s is 2 and Z and Z_1 are –C(O)-.

28. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 27 wherein
Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

29. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 28 wherein Y is a straight or branched C_1-C_{10} alkylene.

30. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 27 wherein
Y is



(IV)

wherein
n is an integer from 0 to 20, and n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;
R^3 and R^4 are independently selected from H or CH_3;
Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20;
X_1 is –WC(O)- or –C(O)W-, wherein W is oxigen, sulfur or NH.

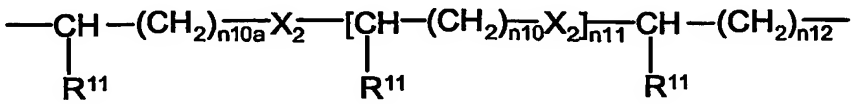
31. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein n2, n3, n4, n5 are equal to 0, n is an integer from 0 to 20, Y^1 is CH_2.

32. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein n, n2, n5 are 1, n3 and n4 are equal to 0, and n1 is 3, Y^1 is $–(CH_2)_{na}$-CH=CH- wherein na is 0, X_1 is –WC(O)- wherein W is

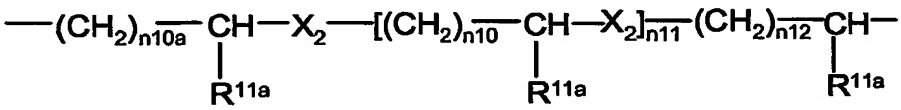
oxigen and X_1 is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the group (OR^4) is bound to the phenyl ring through the $[C]_3$.

33. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 27 wherein

Y is



(VIII)



(IX)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

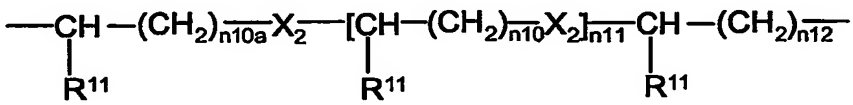
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

34. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 33 wherein

Y is



(VIII)

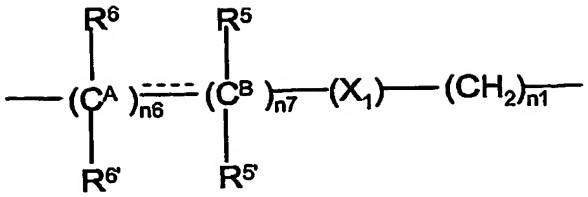
wherein

X_2 is O or S, n10a and n11 are 0, n12 is 1 and R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

35. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 27 wherein

Y is



(VIII)

wherein:

n1 is an integer from 1 to 20;

X_1 is –WC(O)- or a –C(O)W-, wherein W is oxigen, sulfur or NH.

n6 is an integer from 1 to 20 and n7 is an integer from 0 to 20, R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

36. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 35 wherein

n1 is 3, n6 and n7 are 1;

X_1 is –WC(O)- wherein W is sulfur;

R^5, $R^{5'}$ and $R^{6'}$are H, R^6 is $NHCOCH_3$;

with the proviso that the $–ONO_2$ group is bound to the $-(CH_2)_{n1}-$ group.

37. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein s is 1, Z is H and Z_1 are –C(O)-.

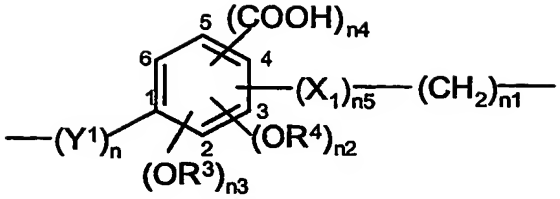
38. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein

Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

39. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 38 wherein Y is a straight or branched C_1-C_{10} alkylene.

40. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20, and n1 is an integer from 1 to 20;

n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

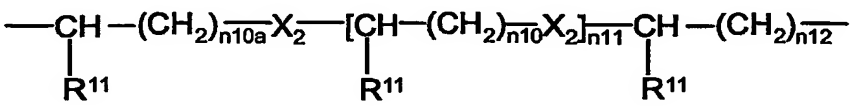
X_1 is $-WC(O)-$ or $-C(O)W-$, wherein W is oxigen, sulfur or NH.

41. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 40 wherein n2, n3, n4, n5 are equal to 0, n is an integer from 0 to 20, Y^1 is CH_2.

42. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 40 wherein n, n2, n5 are 1, n3 and n4 are equal to 0, and n1 is 3, Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0, X_1 is $-WC(O)-$ wherein W is oxigen and X_1 is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the group (OR^4) is bound to the phenyl ring through the $[C]_3$.

43. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein

Y is



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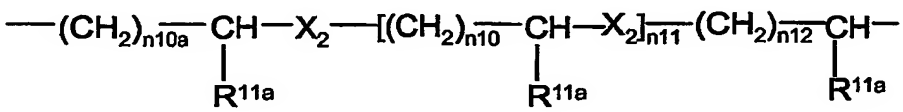


(IX)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

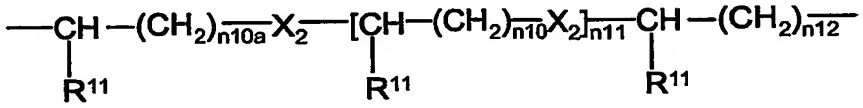
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

44. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 43 wherein

Y is



(VIII)

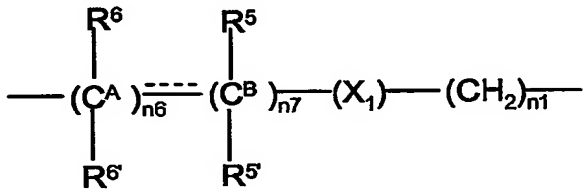
wherein

X_2 is O or S, n10a and n11 are 0, n12 is 1 and R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

45. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein

Y is



(VIII)

wherein:

n1 is an integer from 1 to 20;

X_1 is –WC(O)- or a –C(O)W-, wherein W is oxigen, sulfur or NH.

n6 is an integer from 1 to 20 and n7 is an integer from 0 to 20, R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

46. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 45 wherein

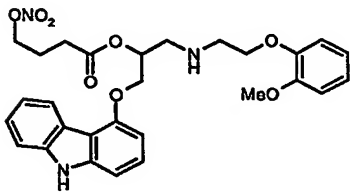
n1 is 3, n6 and n7 are 1;

X_1 is –WC(O)- wherein W is sulfur;

R^5, $R^{5'}$ and $R^{6'}$are H, R^6 is $NHCOCH_3$;

with the proviso that the $-ONO_2$ group is bound to the $-(CH_2)_{n1}-$.

47. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3-12 selected from the group consisting of



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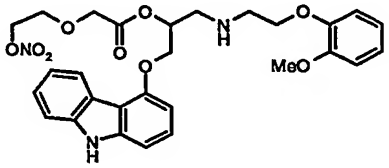

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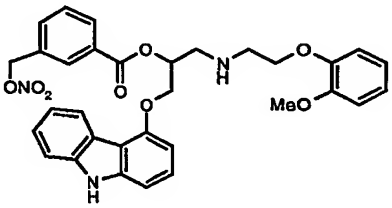

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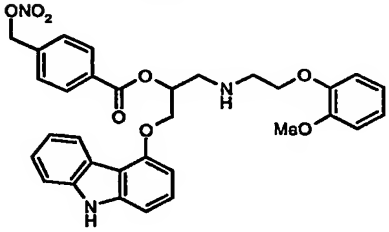

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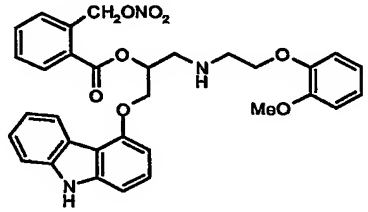

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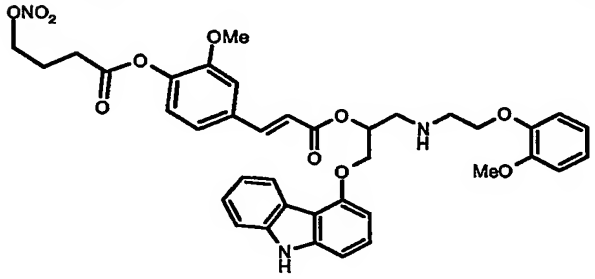

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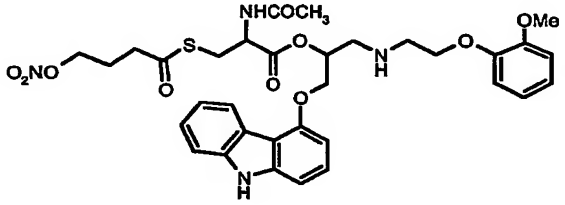

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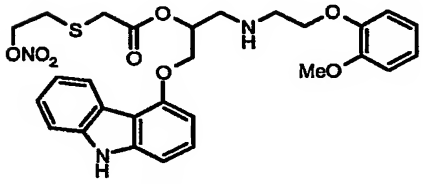

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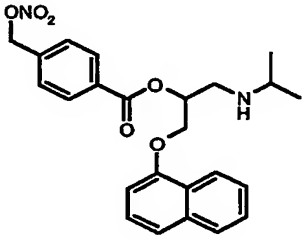

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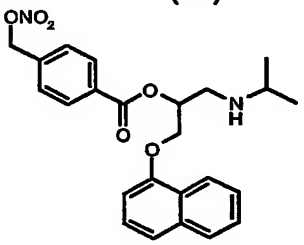

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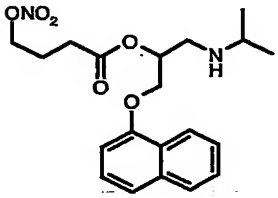

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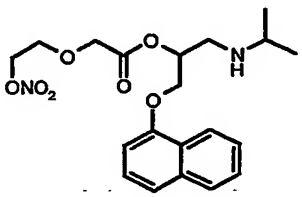

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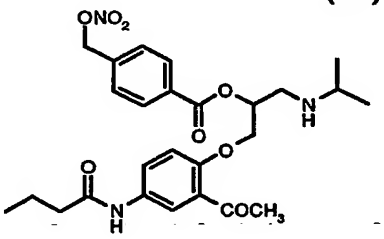

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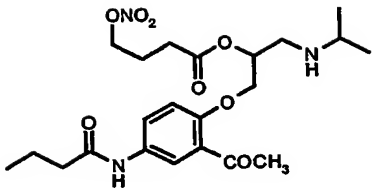

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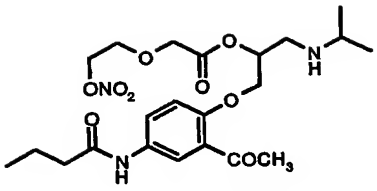

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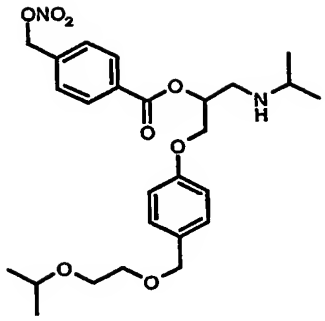

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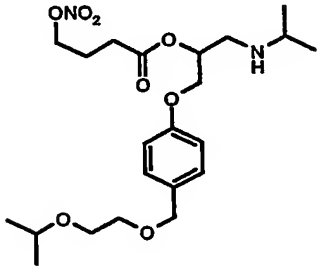

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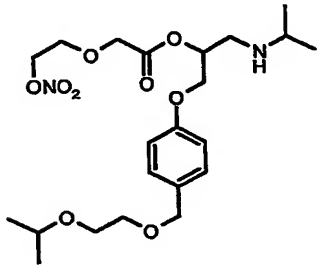

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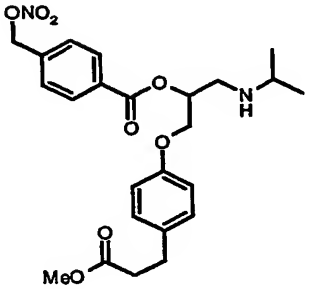

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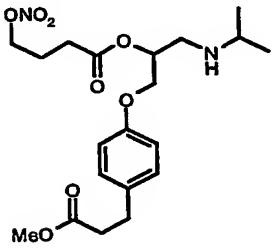

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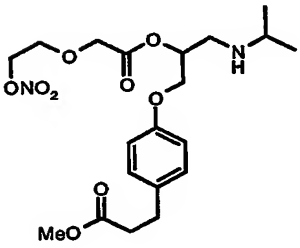

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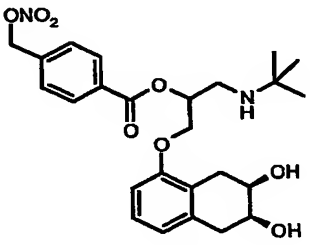

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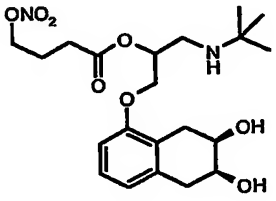

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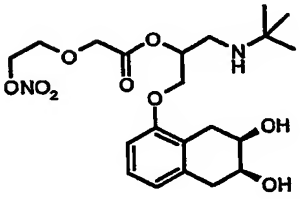

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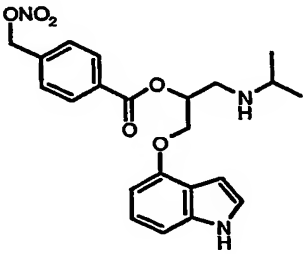

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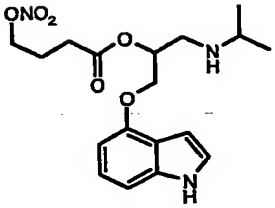

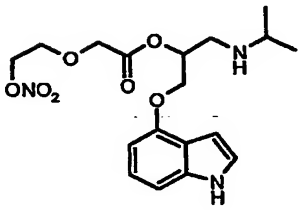

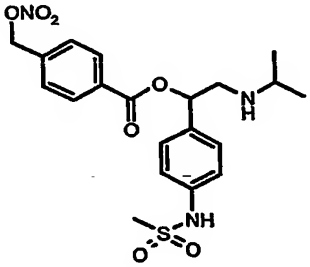

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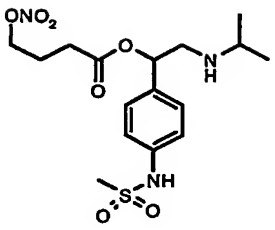

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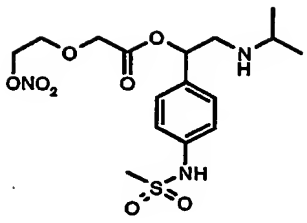

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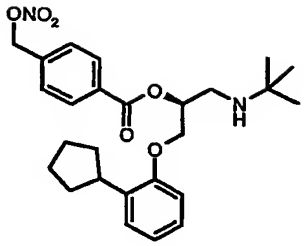

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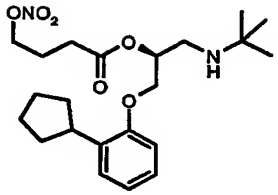

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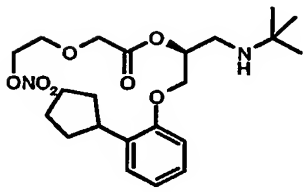

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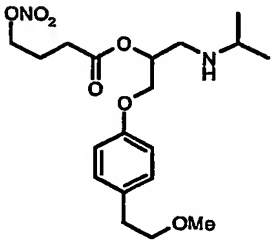

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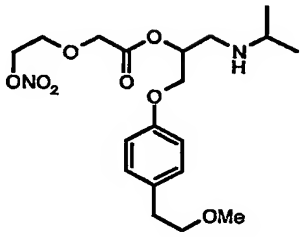

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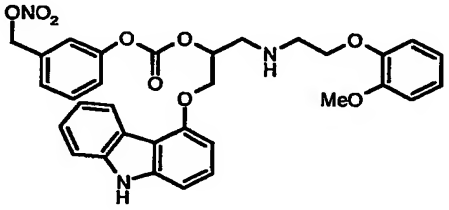
48. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 13–17 selected from the group consisting of



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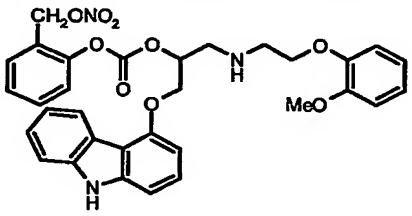

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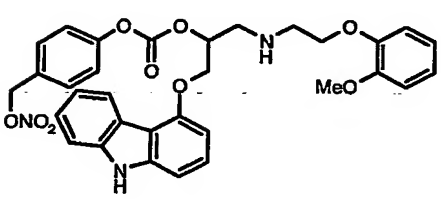

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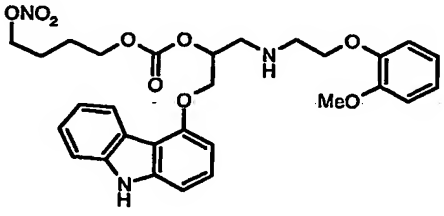

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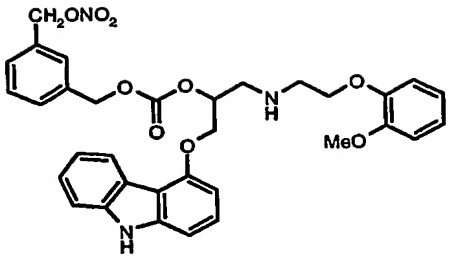

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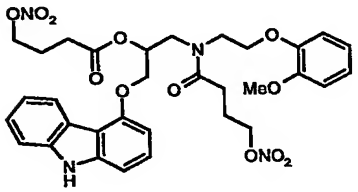
49. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 27–36 selected from the group consisting of



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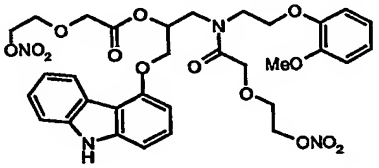

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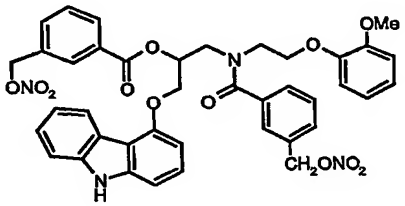

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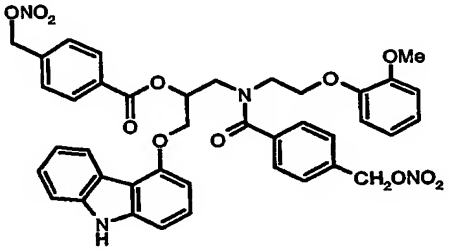

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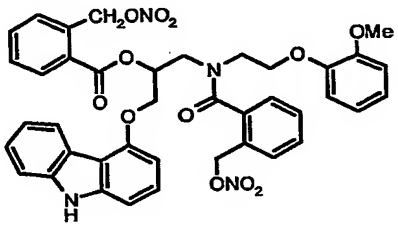

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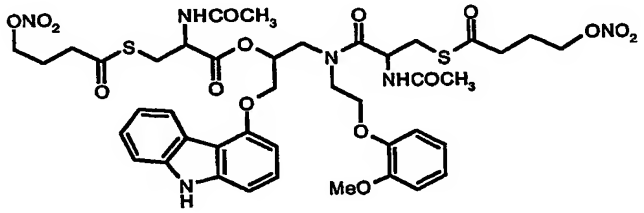

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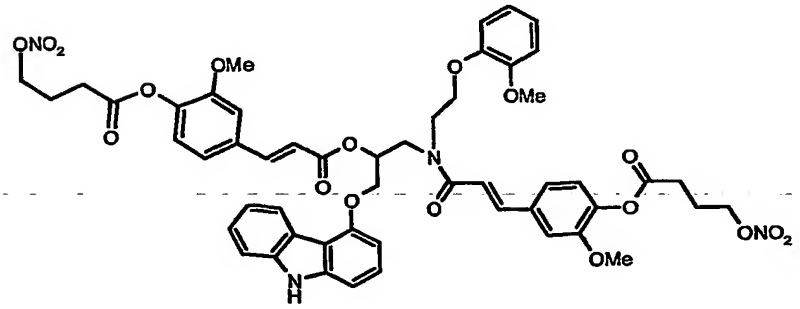

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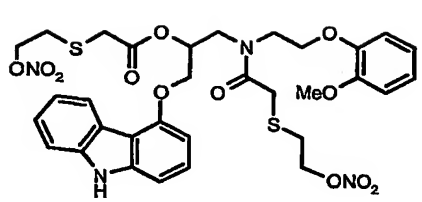

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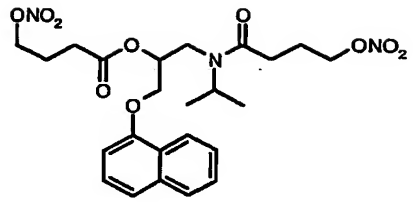

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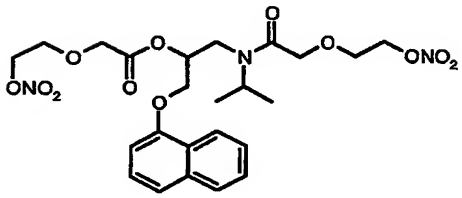

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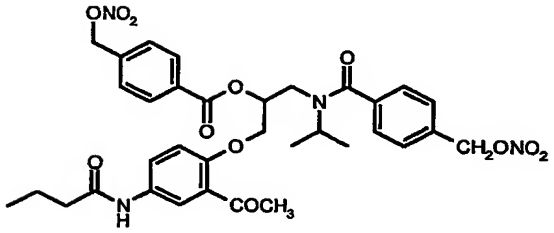

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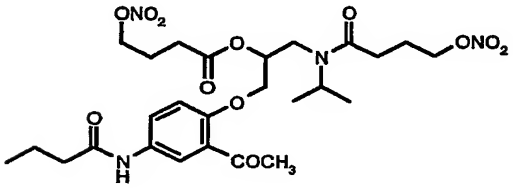

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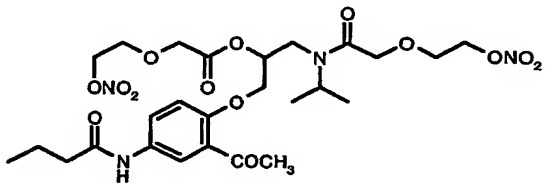

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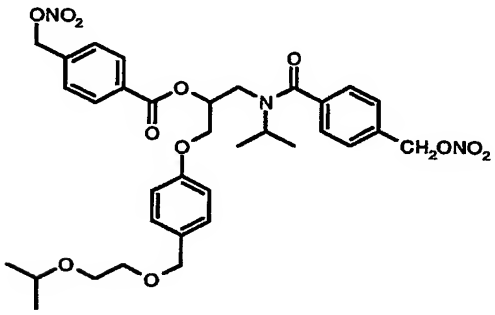

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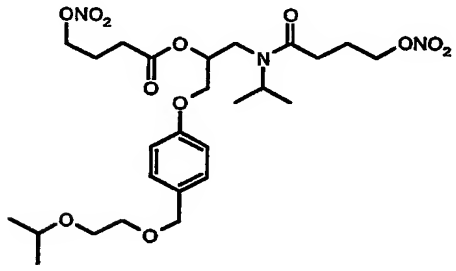

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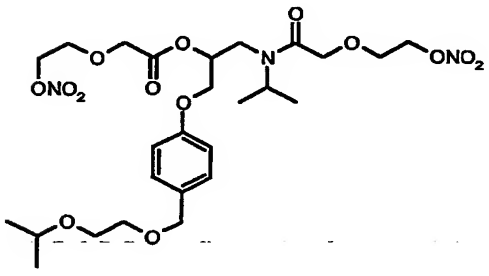

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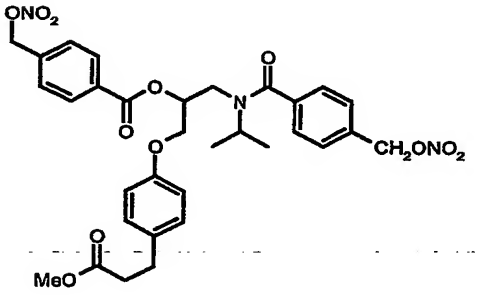

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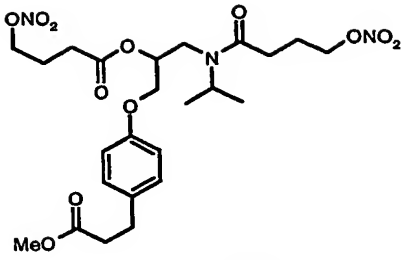

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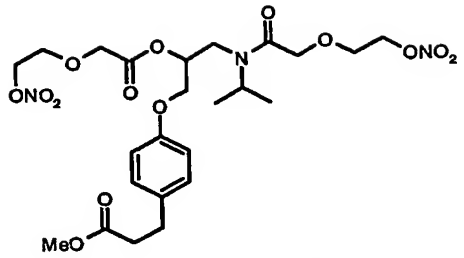

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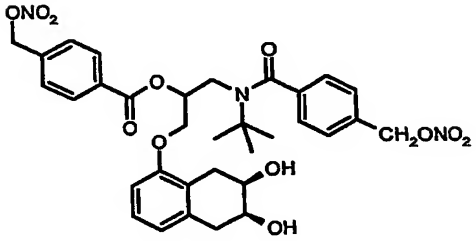

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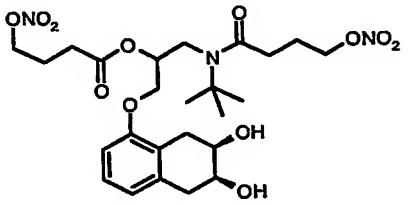

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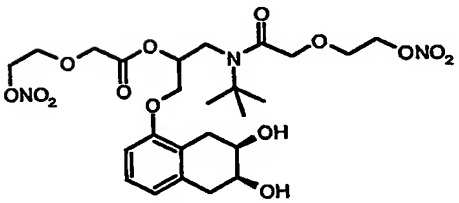

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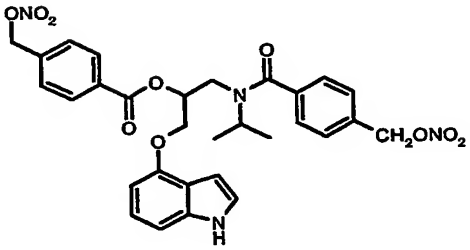

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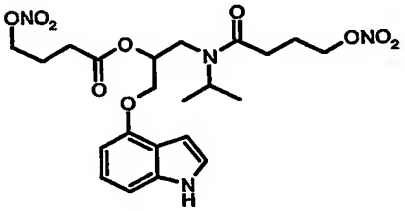

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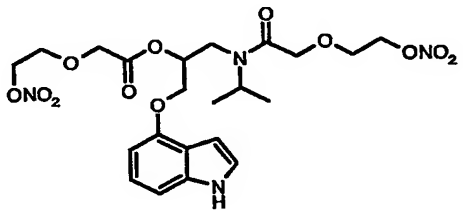

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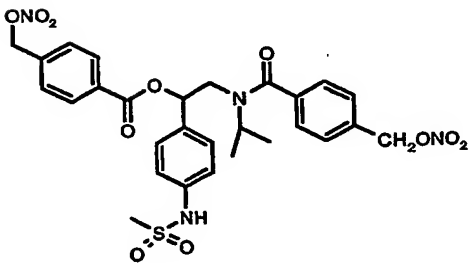

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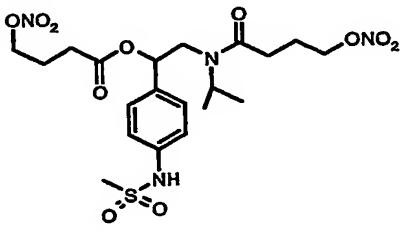

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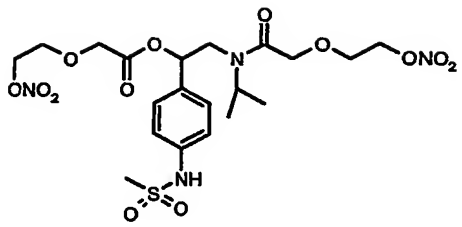

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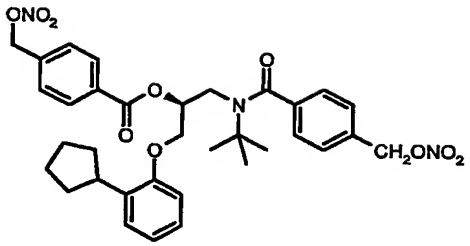

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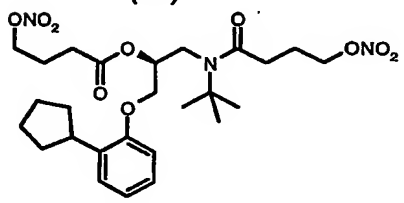

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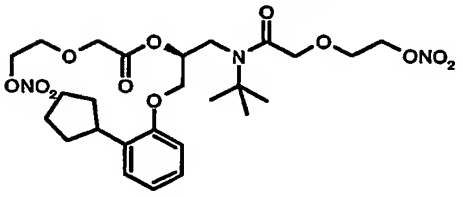

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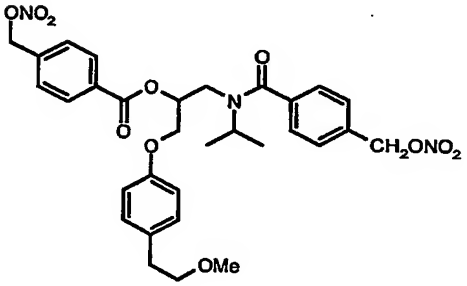

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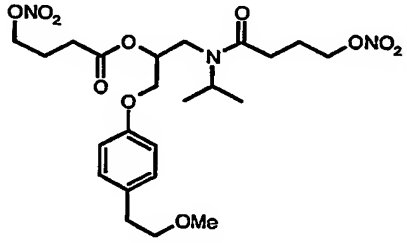

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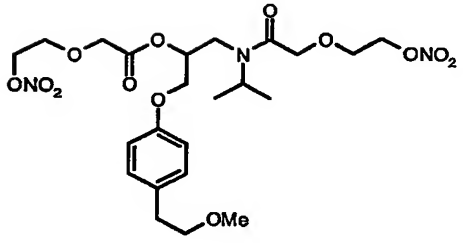
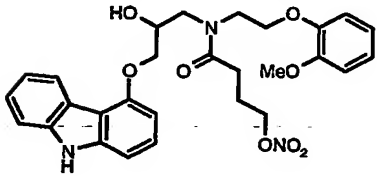


(107)

50. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 37-46 selected from the group consisting of



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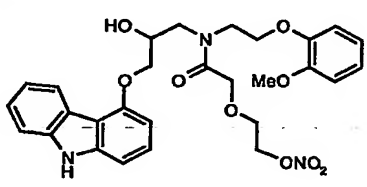

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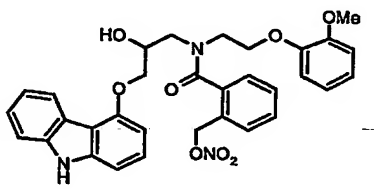

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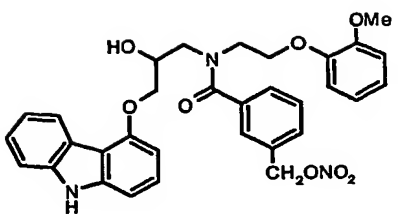

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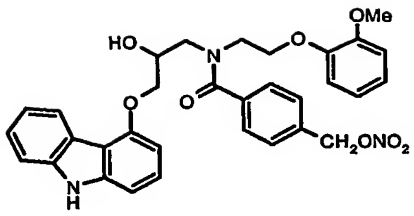

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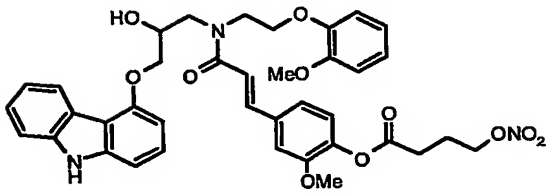

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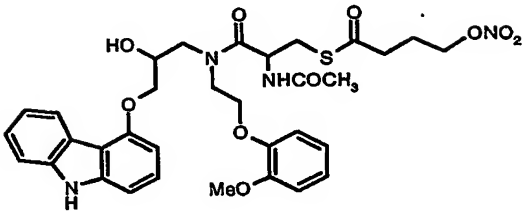

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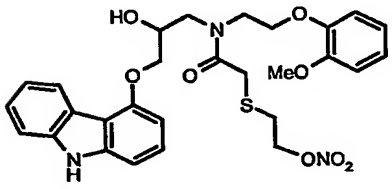

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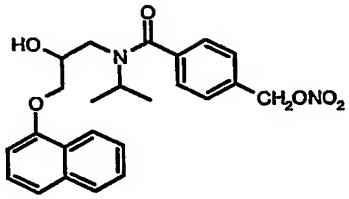

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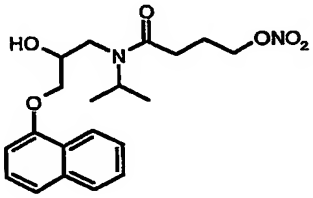

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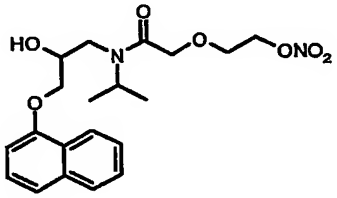

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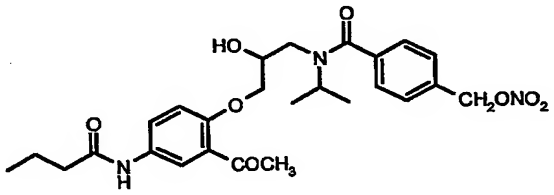

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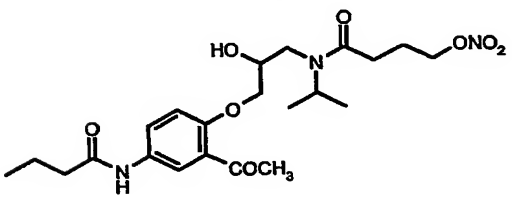

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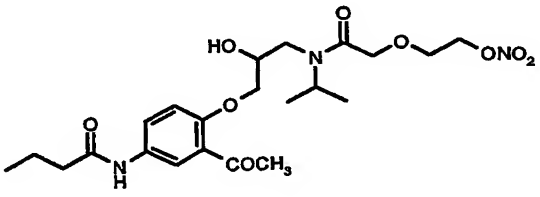

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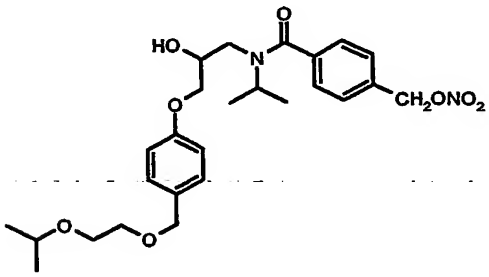

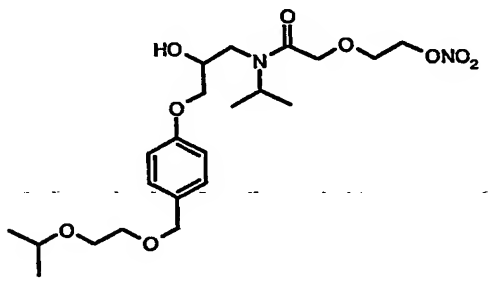

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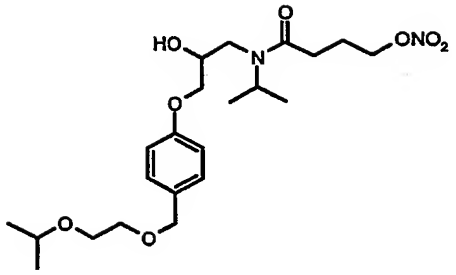

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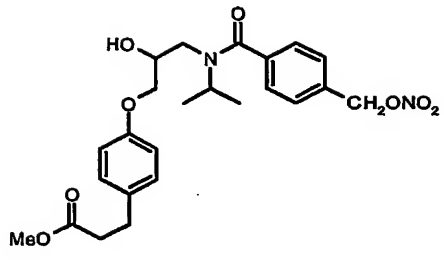

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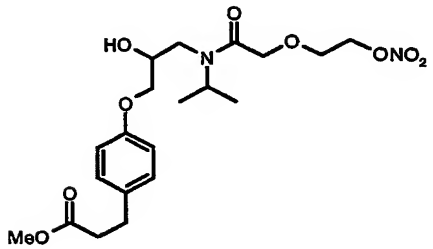

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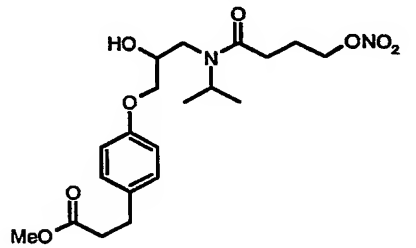

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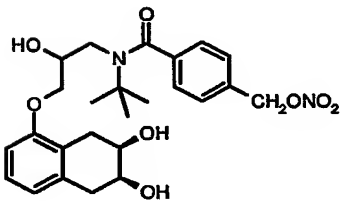

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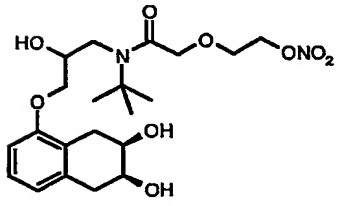

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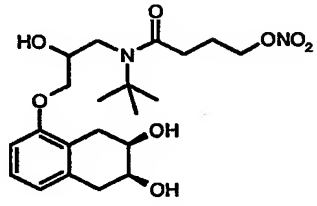

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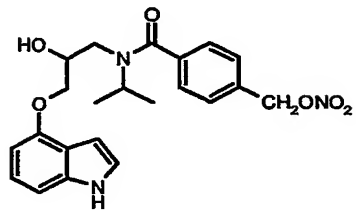

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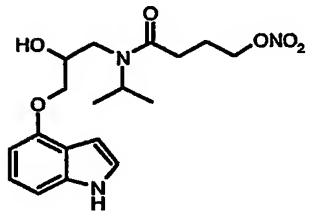

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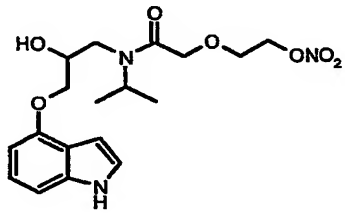

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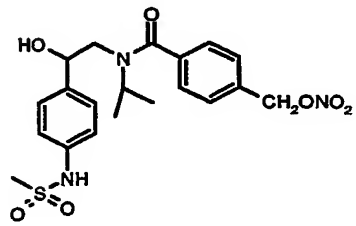

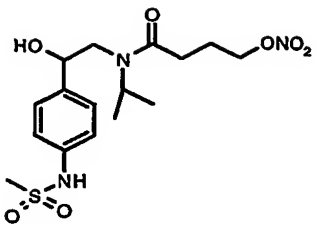

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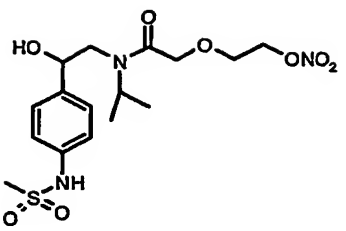

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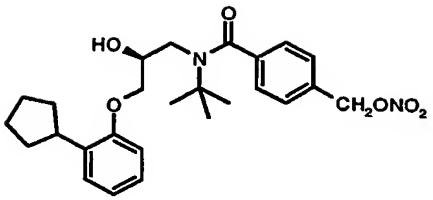

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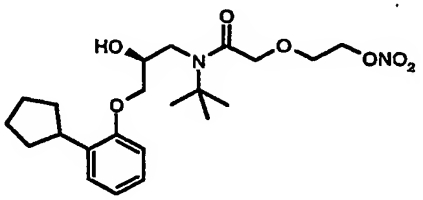

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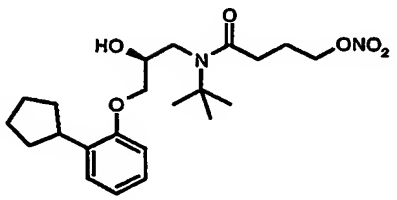

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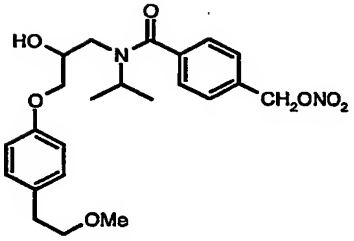

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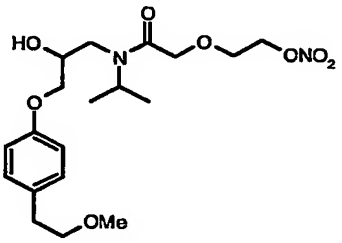

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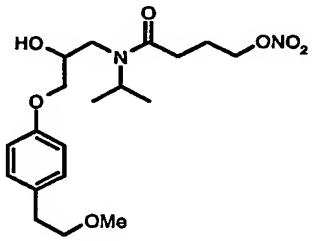

(109)

51. 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl]amino]-2-propanoate and the enantiomers, diastereoisomers and pharmaceutically acceptable salts.

52. 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl][(4-nitrooxymethyl)benzoyl]amino]-2-propanoate and the enantiomers, diastereoisomers and pharmaceutically acceptable salts.

53. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanol and the enantiomers, diastereoisomers and pharmaceutically acceptable salts.

54. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1-53, as therapeutical agent.

55. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 1-53 for preparing a drug that can be employed in the treatment or prophylaxis of hypertension, cardiovascular and vascular diseases.

5

56. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 1-53 for preparing a drug that can be employed in the treatment of glaucoma.

10 57. A pharmaceutical composition comprising a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 1-53 and a pharmaceutical acceptable carrier.

Abstract

The present invention relates to β-adrenergic blockers nitrooxyderivatives of general formula (I):

$$A\text{-}(Y\text{-}ONO_2)_s$$

and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache and vascular diseases.

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